(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 3 May 2001 (03.05.2001)

PCT

English

(10) International Publication Number WO 01/30991 A2

(51) International Patent Classification⁷: C12N 15/00

(21) International Application Number: PCT/US00/23021

(22) International Filing Date: 22 August 2000 (22.08.2000)

(26) Publication Language: English

(30) Priority Data:

(25) Filing Language:

09/426,290 25 October 1999 (25.10.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US 09/426,290 (CIP) Filed on 25 October 1999 (25.10.1999)

- (71) Applicant (for all designated States except US): **DECODE GENETICS EHF.** [IS/IS]; Lynghals 1, IS-110 Reykjavik (IS).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): OLAFSDOTTIR, Berglind, Ran [IS/IS]; Eskihlid 15, IS-105 Reykjavik (IS). GULCHER, Jeffrey [US/US]; Unit M, 130 South Canal Street, Chicago, IL 60606 (US).

- (74) Agents: CARROLL, Alice, O. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

 Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



|/30991 A2

(54) Title: HUMAN NARCOLEPSY GENE

(57) Abstract: The gene for hypocretin (orexin) receptor 2 (HCRTR2), which is associated with narcolepsy, is disclosed. Also described are methods of diagnosis of narcolepsy, pharmaceutical compositions comprising nucleic acids comprising the HCRTR2 gene, as well as methods of therapy of narcolepsy.

-1-

HUMAN NARCOLEPSY GENE

RELATED APPLICATION

5

This application is a Continuation-in-Part of U.S. Serial No. 09/426,290, filed October 25, 1999, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Narcolepsy, a disorder which affects approximately 1 in 2,000 individuals, is characterized by daytime sleepiness, sleep fragmentation, and symptoms of abnormal rapid eye movement (REM) sleep that include cataplexy (loss of muscle 10 tone), sleep paralysis, and hypnagogic hallucinations (Aldrich, M.S., Neurology 42:34-43 (1992); Siegel, J.M., Cell 98:409-412 (1999)). In humans, susceptibility to narcolepsy has been associated with a specific human leukocyte antigen (HLA) alleles, including DQB1*0602 (Mignot, E., Neurology 50:S16-22 (1998); Kadotani, H. et al., Genome Res. 8:427-434 (1998); Faraco, J. et al., J. Hered. 90:129-132 (1999)); however, attempts to verify narcolepsy as an autoimmune disorder have 15 failed (Mignot, E. et al., Adv. Neuroimmunol. 5:23-37 (1995); Mignot, E., Curr. Opin. Pulm. Med. 2:482-487 (1996)). In a canine model of narcolepsy, the disorder is transmitted as an autosomal recessive trait, canarc-1 (Foutz, A.S. et al., Sleep 1:413-421 91979); Baker, T.L. and Dement, W.C., Brain Mechanisms of Sleep (D.J. McGinty et al., eds., New York: Raven Press, pp. 199-233 (1985)). The possibility 20 of linkage between canarc-1 and the canine major histocompatibility complex has been excluded (Mignot, E. et al., Proc. Natl. Acad. Sci. USA 88:3475-3478 (1991)).

WO 01/30991

20

25

PCT/US00/23021

A mutation in the hypocretin (orexin) receptor 2 gene in canines has been identified in narcolepsy (Lin, L. et al., Cell 98:365-376 (1999));

Hypocrexins/orexins (orexin-A and -B) are neuropeptides associated with regulation of food consumption (de Lecea, L., et al., Proc. natl. Acad. Sci. USA 95:322-327 (1998); Sakurai, T. et al., Cell 92:573-585 (1998)) as well as other possible functions (Peyron, C. et al., J. Neurosci. 18:9996-10015 (1998)). Human cDNA of receptors for orexins have been cloned (Sakurai, T. et al., Cell 92:573-585 (1998)).

-2-

Diagnosis of narcolepsy is difficult, as it is necessary to distinguish

narcolepsy from other conditions such as chronic fatigue syndrome or other sleep
disorders (Ambrogetti, A. and Olson, L.C., *Med. J. Aust. 160*:426-429 (1994);
Aldrich, M.S., *Neurology 50*:S2-7 (1998)). Methods of diagnosing narcolepsy
based on specific criteria would facilitate identification of the disease, reduce the
time and expense associated with diagnosis, and expedite commencement of
treatment.

however, full human genes for the orexin receptors have not yet been identified.

SUMMARY OF THE INVENTION

As described herein, a full gene for the human hypocretin (orexin) receptor 2 (HCRTR2) has been identified. The sequence of the HCRTR2 gene as described herein is shown in Figure 1 (SEQ ID NO: 1). Accordingly, this invention pertains to an isolated nucleic acid molecule containing the HCRTR2 gene. The invention also relates to DNA constructs comprising the nucleic acid molecules described herein operatively linked to a regulatory sequence, and to recombinant host cells, such as bacterial cells, fungal cells, plant cells, insect cells and mammalian cells, comprising the nucleic acid molecules described herein operatively linked to a regulatory sequence. The invention also pertains to methods of diagnosing narcolepsy in an individual. The methods include detecting the presence of a mutation in the HCRTR2 gene. The invention additionally pertains to pharmaceutical compositions comprising the HCRTR2 nucleic acids of the invention. The invention further pertains to methods of treating narcolepsy, by administering HCRTR2 nucleic acids

-3-

of the invention or compositions comprising the HCRTR2 nucleic acids. The methods of the invention allow the accurate diagnosis of narcolepsy and reduce the need for time-consuming and expensive sleep laboratory assessments.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A to Fig. 1AY depict the sequence of the human orexin receptor 2 gene (SEQ ID NO:1) and the encoded receptor (SEQ ID NO:2).

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings

10 DETAILED DESCRIPTION OF THE INVENTION

15

The present invention relates to a human hypocretin (orexin) receptor 2 (HCRTR2) gene, and the relationship of the gene to narcolepsy. As described herein, Applicants have isolated the HCRTR2 gene. The gene and its products are implicated in the pathogenesis of narcolepsy, as mutations in a closely related receptor, hypocretin (orexin) receptor 2, have been associated with the presence of narcolepsy in a well-established canine model of narcolepsy (Lin, L. et al., Cell 98:365-376 (1999)).

NUCLEIC ACIDS OF THE INVENTION

Accordingly, the invention pertains to an isolated nucleic acid molecule

containing the human HCRTR2 gene. The term, "HCRTR2 gene," refers to an
isolated genomic nucleic acid molecule that encodes the human hypocretin (orexin)
receptor 2. As used herein, the term, "genomic nucleic acid molecule" indicates that
the nucleic acid molecule contains introns and exons as are found in genomic DNA
(i.e., not cDNA). The nucleic acid molecules can be double-stranded or singlestranded; single stranded nucleic acid molecules can be either the coding (sense)
strand or the non-coding (antisense) strand. The nucleic acid molecule can
additionally contain a marker sequence, for example, a nucleotide sequence which
encodes a polypeptide, to assist in isolation or purification of the polypeptide. Such

10

15

20

25

30

sequences include, but are not limited to, those which encode a glutathione-S-transferase (GST) fusion protein and those which encode a hemagglutinin A (HA) peptide marker from influenza. In a preferred embodiment, the nucleic acid molecule has the sequence shown in the Figure (SEQ ID NO:1).

As used herein, an "isolated" or "substantially pure" gene or nucleic acid molecule is intended to mean a gene which is not flanked by nucleotide sequences which normally (in nature) flank the gene (as in other genomic sequences). Thus, an isolated gene can include a gene which is synthesized chemically or by recombinant means. Thus, recombinant DNA contained in a vector are included in the definition of "isolated" as used herein. Also, isolated nucleotide sequences include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. Such isolated nucleotide sequences are useful in the manufacture of the encoded protein, as probes for isolating homologous sequences (e.g., from other mammalian species), for gene mapping (e.g., by *in situ* hybridization with chromosomes), or for detecting expression of the HCRTR2 gene in tissue (e.g., human tissue), such as by Northern blot analysis.

The present invention also encompasses variations of the nucleic acid sequences of the invention. Such variations can be naturally-occurring, such as in the case of allelic variation, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion and substitution of one or more nucleotides which can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably, the nucleotide or amino acid variations are silent or conserved; that is, they do not alter the characteristics or activity of the hypocretin (orexin) receptor 2.

Other alterations of the nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates), charged linkages (e.g., phosphorothioates, phosphorodithioates), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen),

10

15

20

25

30

chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequences via hydrogen bonding and other chemical interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also relates to fragments of the isolated nucleic acid molecules described herein. The term "fragment" is intended to encompass a portion of a nucleic acid sequence described herein which is from at least about 25 contiguous nucleotides to at least about 50 contiguous nucleotides or longer in length. One or more introns can also be present. Such fragments are useful as probes, e.g., for diagnostic methods, as described below and also as primers or probes. Particularly preferred primers and probes selectively hybridize to a nucleic acid molecule containing the HCRTR2 gene described herein.

The invention also pertains to nucleic acid molecules which hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (e.g., nucleic acid molecules which specifically hybridize to a nucleic acid containing the HCRTR2 gene described herein). Hybridization probes are oligonucleotides which bind in a base-specific manner to a complementary strand of nucleic acid. Suitable probes include polypeptide nucleic acids, as described in (Nielsen *et al.*, *Science* 254, 1497-1500 (1991)).

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (e.g., under high stringency conditions). "Stringency conditions" for hybridization is a term of art which refers to the incubation and wash conditions, e.g., conditions of temperature and buffer concentration, which permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be perfectly (i.e., 100%) complementary to the second, or the first and second may share some degree of complementarity which is less than perfect (e.g., 60%, 75%, 85%, 95%). For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity.

15

20

25

30

-6-

PCT/US00/23021

"High stringency conditions", "moderate stringency conditions" and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6 in Current Protocols in Molecular Biology (Ausubel, F.M. et al., "Current Protocols in Molecular Biology", John Wiley & Sons, (1998)) the teachings of which are hereby incorporated by reference. The exact conditions which determine the stringency of hybridization depend not only on ionic strength (e.g., 0.2XSSC, 0.1XSSC), temperature (e.g., room temperature, 42°C, 68°C) and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, high, moderate or low stringency conditions can be determined empirically. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize (e.g., selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause, M.H. and S.A. Aaronson, *Methods in Enzymology, 200*:546-556 (1991). Also, in, Ausubel, *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of ~17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2XSSC/0.1% SDS for 10 min at room temperature; a moderate

WO 01/30991

5

10

15

20

25

30

-7-

stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2XSSC/0.1% SDS for 15 min at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1XSSC/0.1%SDS for 15 min at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

PCT/US00/23021

Hybridizable nucleic acid molecules are useful as probes and primers, e.g., for diagnostic applications, as described below. As used herein, the term "primer" refers to a single-stranded oligonucleotide which acts as a point of initiation of template-directed DNA synthesis under appropriate conditions (e.g., in the presence of four different nucleoside triphosphates and an agent for polymerization, such as, DNA or RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. The appropriate length of a primer depends on the intended use of the primer, but typically ranges from 15 to 30 nucleotides. Short primer molecules generally require cooler temperatures to form sufficiently stable hybrid complexes with the template. A primer need not reflect the exact sequence of the template, but must be sufficiently complementary to hybridize with a template. The term "primer site" refers to the area of the target DNA to which a primer hybridizes. The term "primer pair" refers to a set of primers including a 5' (upstream) primer that hybridizes with the 5' end of the DNA sequence to be amplified and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

The invention also pertains to nucleotide sequences which have a substantial identity with the nucleotide sequences described herein; particularly preferred are nucleotide sequences which have at least about 70%, and more preferably at least about 80% identity, and even more preferably at least about 90% identity, with nucleotide sequences described herein. Particularly preferred in this instance are nucleotide sequences encoding hypocretin (orexin) receptor 2.

-8-

To determine the percent identity of two nucleotide sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first nucleotide sequence). The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions x 100).

10 The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin et al. (Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993)). Such an algorithm is incorporated into the NBLAST program which can be used to identify sequences having the desired identity to nucleotide sequences of the 15 invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (Nucleic Acids Res, 25:3389-3402 (1997)). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. See http://www.ncbi.nlm.nih.gov. In one embodiment, parameters for sequence 20 comparison can be set at W=12. Parameters can also be varied (e.g., W=5 or W=20). The value "W" determines how many continuous nucleotides must be identical for the program to identify two sequences as containing regions of identity.

The invention also provides expression vectors containing a nucleic acid

comprising the HCRTR2 gene, operatively linked to at least one regulatory
sequence. Many such vectors are commercially available, and other suitable vectors
can be readily prepared by the skilled artisan. "Operatively linked" is intended to
mean that the nucleic acid sequence is linked to a regulatory sequence in a manner
which allows expression of the nucleic acid sequence. Regulatory sequences are artrecognized and are selected to produce a hypocretin (orexin) receptor 2.
Accordingly, the term "regulatory sequence" includes promoters, enhancers, and

WO 01/30991

other expression control elements such as those described in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). For example, the native regulatory sequences or regulatory sequences native to the transformed host cell can be employed. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the receptor desired to be expressed. For instance, the gene of the present invention can be expressed by ligating the gene into a vector suitable for expression in either prokaryotic cells, eukaryotic cells or both (see, for example, Broach, et al., Experimental Manipulation of Gene Expression, ed. M. 10 Inouye (Academic Press, 1983) p. 83; Molecular Cloning: A Laboratory Manual, 2nd Ed., ed. Sambrook et al. (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17). Typically, expression constructs will contain one or more selectable markers, including, but not limited to, the gene that encodes dihydrofolate reductase and the genes that confer resistance to neomycin, tetracycline, ampicillin, chloramphenicol, kanamycin and streptomycin resistance. Vectors can also include, 15 for example, an autonomously replicating sequence (ARS), expression control sequences, ribosome-binding sites, RNA splice sites, polyadenylation sites, transcriptional terminator sequences, secretion signals and mRNA stabilizing sequences.

20 Prokaryotic and eukaryotic host cells transformed by the described vectors are also provided by this invention. For instance, cells which can be transformed with the vectors of the present invention include, but are not limited to, bacterial cells such as *E. coli* (e.g., *E. coli* K12 strains), *Streptomyces*, *Pseudomonas*, *Serratia marcescens* and *Salmonella typhimurium*, insect cells (baculovirus), including
25 *Drosophila*, fungal cells, such as yeast cells, plant cells and mammalian cells, such as thymocytes, Chinese hamster ovary cells (CHO), and COS cells. The host cells can be transformed by the described vectors by various methods (e.g., electroporation, transfection using calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment;
30 lipofection, infection where the vector is an infectious agent such as a retroviral genome, and other methods), depending on the type of cellular host.

-10-

The nucleic acid molecules of the present invention can be produced, for example, by replication in a suitable host cell, as described above. Alternatively, the nucleic acid molecules can also be produced by chemical synthesis.

The nucleotide sequences of the nucleic acid molecules described herein

(e.g., a nucleic acid molecule comprising SEQ ID NO:1) can be amplified by methods known in the art. For example, this can be accomplished by e.g., PCR. See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H.A. Erlich, Freeman Press, NY, NY, 1992); PCR Protocols: A Guide to Methods and Applications (eds. Innis, et al., Academic Press, San Diego, CA, 1990); Mattila et al., Nucleic Acids Res. 19, 4967 (1991); Eckert et al., PCR Methods and Applications 1, 17 (1991); PCR (eds. McPherson et al., IRL Press, Oxford); and U.S. Patent 4,683,202.

Other suitable amplification methods include the ligase chain reaction (LCR) (see Wu and Wallace, *Genomics* 4, 560 (1989), Landegren *et al.*, *Science* 241, 1077 (1988), transcription amplification (Kwoh *et al.*, *Proc. Natl. Acad. Sci. USA* 86, 1173 (1989)), and self-sustained sequence replication (Guatelli *et al.*, *Proc. Nat. Acad. Sci. USA*, 87, 1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

15

20

25

30

The amplified DNA can be radiolabeled and used as a probe for screening a library or other suitable vector to identify homologous nucleotide sequences. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art recognized methods, to identify the correct reading frame encoding a protein of the appropriate molecular weight. For example, the direct analysis of the nucleotide sequence of homologous nucleic acid molecules of the present invention can be accomplished using either the dideoxy chain termination method or the Maxam - Gilbert method (see Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd Ed., CSHP, New York 1989); Zyskind *et al.*, *Recombinant DNA Laboratory*

-11-

Manual, (Acad. Press, 1988)). Using these or similar methods, the protein(s) and the DNA encoding the protein can be isolated, sequenced and further characterized.

METHODS OF DIAGNOSIS

10

15

20

25

30

The nucleic acids and the proteins described above can be used to detect, in an individual, a mutation in the HCRTR2 gene that is associated with narcolepsy. In one embodiment of the invention, diagnosis of narcolepsy is made by detecting a mutation in the HCRTR2 gene. The mutation can be the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift mutation; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene; duplication of all or a part of the gene; transposition of all or a part of the gene; or rearrangement of all or a part of the gene. More than one such mutation may be present in a single gene. Such sequence changes cause a mutation in the receptor encoded by the HCRTR2 gene. For example, if the mutation is a frame shift mutation, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated receptor. Alternatively, a mutation associated with narcolepsy can be a synonymous mutation in one or more nucleotides (i.e., a mutation that does not result in a change in the receptor encoded by the HCRTR2 gene, such as a mutation in an intron or an untranslated portion of the gene). Such a polymorphism may alter splicing sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the gene. A HCRTR2 gene that has any of the mutations described above is referred to herein as a "mutant gene." It is likely that a mutation in the HCRTR2 gene is associated with narcolepsy in humans because of the association between a mutation in the HCRTR2 gene and narcolepsy in dogs (Lin, L. et al., Cell 98:365-376 (1999), the entire teachings of which are incorporated herein by reference). In a preferred

10

15

20

25

30

-12-

PCT/US00/23021

embodiment, the mutation in the HCRTR2 gene is to a deletion mutation, for example, a deletion that corresponds to the deletions found in the hypocretin (orexin) receptor 2 in narcoleptic dogs as described by Lin *et al.*, *supra* (e.g., a deletion of one or more exons, such as a deletion of the fourth exon, that can be caused by insertion of one or more nucleotides upstream of the splice site of the exon, or a deletion of exon 6, that can be caused by a G to A transition in the splice junction consensus sequence). In another preferred embodiment, the mutation in the HCRTR2 gene is mutation that effects a "knockout" of the entire gene, such as deletion of the first exon as described by Chemelli, R.M. *et al*, (*Cell 98*:437-451 (1999), the entire teachings of which are incorporated herein). In a third preferred embodiment, the mutation in the HCRTR2 gene is a mutation in an intron, that affects splicing (joining of exons) during translation of the HCRTR2 gene.

In a first method of diagnosing narcolepsy, hybridization methods, such as Southern analysis, are used (see Current Protocols in Molecular Biology, Ausubel, F. et al., eds., John Wiley & Sons, including all supplements through 1999). For example, a test sample of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having (or carrying a defect for) narcolepsy (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source which contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, placenta, gastrointestinal tract or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a mutation in the HCRTR2 gene is present. The presence of the mutation can be indicated by hybridization of the gene in the test sample to a nucleic acid probe. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe contains at least one mutation in the HCRTR2 gene. The probe can be one of the nucleic acid molecules described above (e.g., the gene, a vector comprising the gene, etc.)

To diagnose narcolepsy by hybridization, a hybridization sample is formed by contacting the test sample containing a HCRTR2 gene, with at least one nucleic WO 01/30991

5

10

15

20

25

30

acid probe. The hybridization sample is maintained under conditions which are sufficient to allow specific hybridization of the nucleic acid probe to the HCRTR2 gene. "Specific hybridization", as used herein, indicates exact hybridization (e.g., with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

-13-

PCT/US00/23021

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and the HCRTR2 gene in the test sample, then the HCRTR2 gene has the mutation that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a mutation in the HCRTR2 gene, and is therefore diagnostic for narcolepsy.

In another hybridization method, Northern analysis (see Current Protocols in Molecular Biology, Ausubel, F. et al., eds., John Wiley & Sons, supra) is used to identify the presence of a mutation associated with narcolepsy. For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a mutation in the HCRTR2 gene, and is therefore diagnostic for narcolepsy

For representative examples of use of nucleic acid probes, see, for example, U.S. Patents No. 5,288,611 and 4,851,330. Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P.E. *et al.*, *Bioconjugate Chemistry*, 1994, 5, American Chemical Society, p. 1 (1994). The PNA probe can be designed to specifically hybridize to a gene having a polymorphism associated with autoimmune disease. Hybridization of the PNA probe to the HCRTR2 gene is diagnostic for narcolepsy...

-14-

In another method of the invention, mutation analysis by restriction digestion can be used to detect mutant genes, or genes containing polymorphisms, if the mutation or polymorphism in the gene results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify the HCRTR2 gene (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see Current Protocols in Molecular Biology, supra). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the mutation in the HCRTR2 gene, and therefore indicates the presence or absence of narcolepsy.

Sequence analysis can also be used to detect specific mutations in the HCRTR2 gene. A test sample of DNA is obtained from the test individual. PCR can be used to amplify the gene, and/or its flanking sequences. The sequence of the HCRTR2 gene, or a fragment of the gene is determined, using standard methods. The sequence of the gene (or gene fragment) is compared with the nucleic acid sequence of the gene, as described above. The presence of a mutation in the

HCRTR2 gene indicates that the individual has narcolepsy.

10

15

20

25

30

Allele-specific oligonucleotides can also be used to detect the presence of a mutation in the HCRTR2 gene, through the use of dot-blot hybridization of amplified proteins with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. et al., (1986), Nature (London) 324:163-166). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, preferably approximately 15-30 base pairs, that specifically hybridizes to the HCRTR2 gene, and that contains a mutation associated with narcolepsy. An allele-specific oligonucleotide probe that is specific for particular mutation in the HCRTR2 gene can be prepared, using standard methods (see Current Protocols in Molecular Biology, supra). To identify mutations in the gene that are associated with narcolepsy, a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of the HCRTR2 gene, and its flanking sequences. The DNA containing the amplified HCRTR2 gene (or fragment of the gene) is dot-

10

15

20

25

blotted, using standard methods (see Current Protocols in Molecular Biology, supra), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified HCRTR2 gene is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a mutation in the HCRTR2 gene, and is therefore indicative of narcolepsy.

Other methods of nucleic acid analysis can be used to detect mutations in the HCRTR2 gene, for the diagnosis of narcolepsy. Representative methods include direct manual sequencing; automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCA); clamped denaturing gel electrophoresis (CDGE) heteoduplex analysis; chemical mismatch cleavage (CMC); RNase protection assays; use of proteins which recognize nucleotide mismatches, such as *E. coli* mutS protein; allele-specific PCR, and other methods.

PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleic acids containing the HCRTR2 gene described herein. For instance, a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (e.g., NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic

-16-

pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

10

15

20

25

30

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devises ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other agents.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The agent may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., pressurized air.

10

15

20

25

30

Agents described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The agents are administered in a therapeutically effective amount. The amount of agents which will be therapeutically effective in the treatment of narcolepsy can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture,

use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (e.g., separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

10

15

20

25

30

The present invention also pertains to methods of therapy for narcolepsy, utilizing the pharmaceutical compositions comprising nucleic acids, as described herein. The therapy is designed to replace/supplement activity of the hypocretin(orexin) receptor 2 in an individual, such as by administering a nucleic acid comprising the HCRTR2 gene or a derivative or active fragment thereof. In one embodiment of the invention, a nucleic acid of the invention is used in the treatment of narcolepsy. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease, and also lessening the severity or frequency of symptoms of the disease. In this embodiment, a nucleic acid of the invention (e.g., the HCRTR2 gene (SEQ ID NO:1)) can be used, either alone or in a pharmaceutical composition as described above. For example, the HCRTR2 gene, either by itself or included within a vector. can be introduced into cells (either in vitro or in vivo) such that the cells produce native HCRTR2 receptor. If necessary, cells that have been transformed with the gene or can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells which, in nature, lack native HCRTR2 expression and activity, or have mutant HCRTR2 expression and activity, can be engineered to express

-19-

HCRTR2 receptors (or, for example, an active fragment of the HCRTR2 receptor). In a preferred embodiment, nucleic acid comprising the HCRTR2 gene, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells which lack native HCRTR2 expression in an animal. In such methods, a cell population can be engineered to inducibly or constitutively express active HCRTR2 receptor. Other gene transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral gene transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (e.g., microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used.

10

15

20

The nucleic acids and/or vectors are administered in a therapeutically effective amount (i.e., an amount that is sufficient to treat the disease, such as by ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount which will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The following Examples are offered for the purpose of illustrating the present invention and are not to be construed to limit the scope of this invention. The teachings of all references cited herein are hereby incorporated herein by reference.

-20-

EXAMPLES

EXAMPLE 1 Identification of the Human Narcolepsy Gene
A human BAC library (RPCI11 human male BAC library; see Osoegawa, K.
et al., Genomics 52:1-8 (1998)) was used. Twenty primers, designed from the
mRNA sequence of the HCRTR2 receptor, were employed to identify clones of
interest. They are set forth in Table 1.

TABLE 1 Primers Used for Hybridization

	#	Name	Primer Sequence	SEQ ID NO:
	1	HCRTR2-1-F	TACTACTAGGCCACGCG	3
	2	HCRTR2-1-R	ACACCAGGAGGAGAAAGCTAC	4
5	3	HCRTR2-2-F	ATCGCCTGTAAAGACAGCAAAG	5
	4	HCRTR2-2-R	AAAGTTACTGAGCCAATGCCTC	6
	5	HCRTR2-3-F	GAGAGGAGCTTGCAGCATTG	7
	6	HCRTR2-3-R	AGGAATTCCTCGTCGTCATAGT	8
	7	HCRTR2-4-F	GAAGAACCACCACATGAGGAC	9
10	8	HCRTR2-4-R	ATCACTTTGCAAAGGGACTGTC	10
	9	HCRTR2-5-F	GTATGCAATCTGTCACCCTTTG	11
	10	HCRTR2-5-R	AATGCAGGAGACAATCCAGATG	12
15	11	HCRTR2-6-F	CAGGCTTAGCCAATAAAACCAC	13
	12	HCRTR2-6-R	GATAAGCCAACACCATGAGACA	14
	13	HCRTR2-7-F	ACAGATCCCTGGAACATCATCT	15
	14	HCRTR2-7-R	CTCGGATCTGCTTTATTTCAGC	16
	15	HCRTR2-8-F	CCAATTAGCATCCTCAATGTGC	17
20	16	HCRTR2-8-R	GTGTGAAAAGGTAAACCAGGCA	18
	17	HCRTR2-9-F	CTCAGTGGAAAATTTCGAGAGG	19
	18	HCRTR2-9-R	GTTGCTGATTTGAGTGGTCAAG	20
	19	HCRTR2-10-F	CTTTCTGAGCAAGTTGTGCTCA	21
	20	HCRTR2-10-R	TACCAGTTTTGAAGTGGTCCTG	22

Initial Study with Large Membranes

Four out of 5 membranes having the whole BAC library, containing a total of approximately 160,000 BAC clones representing an approximately 10-fold coverage of the human genome, were used in hybridization studies with these primers.

Hybridization was performed with a pool of all 20 primers described in Table 1.

PCT/US00/23021

5' End Labeling for Big Membranes

Oligonucleotides were labeled at the 5' end before hybridization, using fresh (less than one month old) [γ^{32} P]ATP (6000 Ci/mmole; 10 μ Ci/ μ l). The following protocol is adjusted for 4 membranes in 2 bottles, containing 2 membranes/30 ml of rapid hyb. Each. Briefly, a labeling mixture was made of DNA (8 pmol/ μ l) (10.0 μ l of the primer pool), 10X buffer (12.0 μ l), T4 PNK (10 u/ μ l) (6.0 μ l), [γ^{32} P]ATP (30.0 μ l, or 600 μ Ci), and water (62.0 μ l) for a final volume of 120 μ l. 20 μ l of labeling mixture was used per 10 ml rapid hybridization reaction. Incubation of the labeling mixture was for 2 hours at 37°C, followed by transfer to ice, spinning down, and mixing with the rapid hybridization solution. The membranes were prehybridized at 42°C before the labeling mix was added. Sixty μ l of the labeling mix was added to each of 2 big bottles containing 2 membranes and 30 ml of rapid hybridization solution.

Hybridization and Washing

10

15

20

25

The membranes were hybridized at 42°C overnight. After overnight, membranes were washed with 6x SSC, 0.1% SDS at room temperature; washed with 6x SSC, 0.1% SDS at 55°C in a shaking waterbath, repeated until the radioactivity of membranes was lower than 6k using 1x sensitivity; and washed with 6x SSC to remove the SDS. The washed membranes were put in a cassette for overnight exposure at -80°C with a MR single emulsion film. Positive clones were identified and gridded on small membranes.

Study of Positive Clones with Small Membranes

After growing the positively-identified clones on several small membranes (to get several copies of membranes containing the same clones), and washing the membranes, hybridization was performed using pairs of primers, instead of a total pool of primers as before. The total number of hybridizations was ten, using different primers against identical copies of membranes containing all positive clones from the first hybridization. The primer pairs are set forth in Table 2; primer numbers indicate the primers shown in Table 1.

WO 01/30991

TABLE 2 Primer Pairs Used for Hybridization

	Reaction number	Primers Used
	1	1 and 2
	2	3 and 4
5	3	5 and 6
	4	7 and 8
	5	9 and 10
10	6	11 and 12
	7	13 and 14
	8	15 and 16
	9	17 and 18
	10	18 and 19

5' End Labeling for Small Membranes

Oligonucleotides were labeled at the 5' end before hybridization, using fresh [γ³²P]ATP (5000 Ci/mmole; 10 μCi/μl). Briefly, a labeling mixture was made of DNA (8 pmol/μl) (1.5 μl), 10X buffer (2.0 μl), T4 PNK (10 u/μl) (1.0 μl), [γ³²P]ATP (3.0 μl), and water (12.5 μl) for a final volume of 20 μl. Incubation of the labeling mixture was for 2.5 hours at 37°C, followed by transfer to ice, spinning down, and mixing with the rapid hybridization solution. Membranes were prewetted in 6X SSC, rolled in a pipette, and excess liquid drained prior to placing the membrane in the tube. Fifty ml Falcon (polypropylene) tubes were used as container for the hybridization. The membranes were prehybridized at 42°C before 20 μl of labeling mix was added to each tube.

Hybridization and Washing

The membranes were hybridized at 42°C overnight. After overnight, membranes were washed as described above. Four clones which were positive for primers designed using the 5' and 3' end of the mRNA were identified. Clone 403B19 was used to characterize the gene.

WO 01/30991

25

30

Sequencing of Narcolepsy Gene in Clone 403B19

Shotgun sequencing was used to obtain the gene sequence.

Preparation of DNA Samples

BAC DNA was isolated using the Plasmix kit from TALENT-VH Bio 5 Limited. Thirty µg of isolated DNA was fragmented by nebulization: a nebulizer (IPI Medical Products, Inc., no. 4207) was modified by removing the plastic cylinder drip ring, cutting off the outer rim of the cylinder, inverting it and placing it back into the nebulizer; the large hole in the top cover (where the mouth piece was attached) was sealed with a plastic stopper; the small hole was connected to a 1/4 10 inch length of Tycon tubing (connected to a compressed air source). A DNA sample was prepared containing 30 μg DNA, 10 X TM buffer (200 μl), sterile glycerol (1 ml), and sterile dd water (q.s.) for a total volume of 2 ml. The DNA sample was nebulized in an ice-water bath for 2 minutes and 40 seconds (pressure bar reading 0.5). The sample was then briefly centrifuged at 2500 rpm to collect the DNA; the 15 entire unit was placed in the rotor bucked of a table top centrifuge (Beckman GPR tabletop centrifuge) fitted with pieces of Styrofoam to cushion the nebulizer. The sample was then distributed into four 1.5 ml microcentrifuge tubes and ethanol precipitated. The Dried DNA pellet was resuspended in 35 μl of 1X TM buffer 20 prior to proceeding with fragment end-repair.

Fragment End Repair, Size Selection and Phosphorylation

The DNA was resuspended in 27 μl of 1X TM buffer. The following materials were added: 10 X kinase buffer (5 μl), 10 mM rATP (5 μl), 0.25 mM dNTPs (7 μl), T4 polynucleotide kinase (1 μl (3 U/μl)), Klenow DNA polymerase (2 μl (5 U/μl)), T4 DNA polymerase (1 μl (3 U/μl)), for a total volume of 48 μl. The mixture was incubated at 37°C for 30 minutes, and then 5 μl of agarose gel loading dye was added. The mixture was then applied to separate wells of a 1% low melting temperature agarose gel and electrophoresed for 30-60 minutes at 100-120 mA. The DNA was then eluted from each sample lane, extracted from the agarose

using Ultrafree-DA columns (Millipore) and then cleaned with Microcon-100 columns (Amicon), precipitated in ethanol, and resuspended in 10 μ l of 10:0.1 TE buffer.

Ligation

5

15

EcoRV-linearized, CIAP-dephosphorylated Bluescript vector was used as a cloning vector. The following reagents were combined in a microcentrifuge tube, and incubated overnight at 4°C: DNA fragments (100-1000 ng), cloning vector (2 μl (10 ng/μl)), 10X ligation buffer (1 μl), T4 DNA ligase (NEB 202L) (1 μl (400 U/μl)), sterile dd water (q.s.), for a total of 10 μl.

10 Transformation of Ligated Products

The ligation products were diluted 1:5 with dd water and used to transform electrocompetent TOP 10F cells (Invitrogen) using GenePulser II (Biorad; voltage, 2.5 W, resistance 100 ohm). Transformants were plated on LB plates with 50 μ l of 4% X-GAL and 50 μ l of 4% IPTG, and ampicillin. Transformants were grown overnight at 37°C, white colonies were picked, grown in a culture of 3 ml LB liquid media plus 200 μ g/ μ l ampicillin for 16-20 hours with shaking. DNA was isolated from the liquid cultures using Autogen 740 Automatic Plasmid Isolation System.

Cycle Sequencing of Isolated Plasmid DNA

Isolated plasmids were then sequenced using the M13 primers: M13-forward (SEQ ID NO:23) TGTAAAACGACGGCCAG; and M13-reverse (SEQ ID NO:24) CAGGAAACAGCTATGAC. For the sequencing reaction, 2.5 µl plasmid template was mixed with 4 µl Big Dye Ready reaction mix (ABI), 1 µl of 8 pM M13 primer, and 2.5 µl dd water. For cycle sequencing, 25 cycles of 96°C for 10 seconds, 50°C for 5 seconds, and 60 °C for 4 minutes were performed, followed by holding at 4°C.

The cycle sequencing reaction products were cleaned by spinning through Sephadex G-50 columns. The eluted cycle sequencing products were then dissolved in 3 µl formamide/dye and 1.5 µl of sample was loaded on ABI 377 automated sequencers. The data was analyzed using Phred and Phrap (Ewing, B. et al., Genome Res. 8:175-

185 (1998); Ewing, B. and Green, P., *Genome Res.* 8:186-194 (1998)), and viewed in Consed viewer (Gordon, D. et al., Genome Res. 8(3):195-202 (1998)).

Analysis of Gene Structure

5

10

20

The *hcrtr-2* gene maps to chromosome 6p11-q11. A total of 168,575 base pairs of contiguous sequence was generated for 403B19 which contained all of the *hcrtr-2* gene. Comparison of the cDNA sequence of *hcrtr-2* (Accession number GI:6006037) and the genomic sequences generated allowed deduction of the intron/exon organization of the gene. The gene contains 7 exons which cover 108,439 bp. The first 10 Gs in the mRNA sequence for *hcrtr-2* were not found in the genomic sequence. It is likely that these Gs were an artifact.

The splice junctions of the *hcrtr-2* gene are set forth in Table 3, and the intron sizes are set forth in Table 4. Exon sequences are represented in uppercase and introns in lowercase. All splice sites conform to the consensus GT-AG rule. SEQ ID NOs are given in the column immediately following each site.

15 Table 3 Splice Junctions of hcrtr-2

	Splice Donor Site	SEQ ID	Splice Acceptor Site	SEQ ID
Hcrtr-2 exon1-2	TCCTGGgtgagt	25	aattagTTTGTG	26
Hcrtr-2 exon2-3	CTACAGgtaatt	27	ctctagACCGTG	28
Hcrtr-2 exon3-4	GGGGTGgtaagt	29	tcctagGTGAAA	30
Hcrtr-2 exon4-5	CGACAGgtatat	31	tttcagATCCCT	32
Hcrtr-2 exon5-6	AAAGAGgtaaaa	33	ctgcagAGTATT	34
Hcrtr-2 exon6-7	TCAGTGgtgagt	35	tgccagGAAAAT	36

Table 4 Intron Sizes of hcrtr-2

Intron	Nucleotides
Intron 1	73,848
Intron 2	6,322
Intron 3	8,327
Intron 4	13,618
Intron 5	2,730
Intron 6	1,779

10 membrane domain G protein linked receptor. Five of the transmembrane regions are by themselves within one exon, two of the transmebrane segments are broken up by introns, and two transmembrane segments fall within the same exon. A survey done one year ago on mammalian G-protein coupled receptors (GPCRs) sequences in GenBank revealed that over 90% of GPCRs genes were intronless in their open 15 reading frame (ORF) (Gentles, A.J. and Karlin, S., *Trends Genet. 15*:47-49 (1999)). Comparison of the intron/exon boundaries of *hcrtr-2* and the genes coding for their most related GPCRs based on sequence similarity showed that the location of the intron/exons boundaries with respect to the transmembrane domains is only partially conserved among the receptors (Sakurai, T. *et al.*, *Cell 92*:573-585 (1998)).

20 Computer analysis of sequence data

Analysis of the genomic sequence of *hcrtr-2* using the program RepeatMasker (http://ftp.genome.washington.edu/cgi-bin/RepeatMasker) showed that the sequence containing the *hcrtr-2* genomic sequence is 38.27% repeat sequences and the GC content is 35.3%.

The sequences of the genes were analyzed using the program GeneMiner (Óskarsson and Pálsson, unpublished), which combines the results of 5 exon prediction programs; FGENE (Solovyev, V. and Salamov, A., *Ismb* 5:294-302 (1997)), Genscan (Burge, C. and Karlin, S., *J. Mol. Biol.* 268:78-94 (1997)),

HMMgene (Krogh, A., *Ismb* 5:179-186 (1997)), MZEF (Zhang, M.Q., *Proc. Natl. Acad. Sci. USA* 94:565-8 (1997)) and Xpound (Thomas, A. and Skolnick, M.H., *IMA J. Math Appl. Med. Biol.* 11:149-160 (1994)). For *hcrtr-2*, 3 out of 5 programs predicted the 3' end of exon 1, only one program predicted the 7th exon and for the internal exons, there were at least two programs that predicted each of them exactly or in part.

The promoter sequences of the genes have not yet been characterized. The Promoter Prediction by Neural Network (http://www.fruitfly.org/seq_tools/promoter.html) predicted promoters that are at least 140 bp upstream of the 5´UTR of *hcrtr-2*, indicating that either a part of the 5´UTR is missing in the published mRNA sequence or the real promoters are not detected by the program.

Analysis of Population for Polymorphisms

10

30

in nucleic acid samples from 47 patients and 75 control individuals. The patient population consisted of patients of Icelandic and US origin. The control population consisted of Icelandic controls, CEPH (Centre d'Etude du Polymorphisme Humain) individuals from Utah and France, and US samples of various ethnic origins. The African-American/Caucasian ratios were similar between patients and controls. All narcoleptic subjects complained of excessive daytime sleepiness (EDS). Approximately 66% of the patients had cataplexy, 24% did not and 10% did not have attainable records of cataplexy status. Narcoleptic subjects without cataplexy had Multiple Sleep Latency Tests showing mean sleep latencies of less than 10 minutes and REM sleep in at least 2 naps. Subjects did not take any drugs affecting sleep for at least 10 days before their sleep studies.

To analyze the nucleic acids, DNA from patient and control blood samples were isolated by the method of Kunkel (Kunkel, L.M. et al., Proc. Natl. Acad. Sci. USA 74:1245-9 (1977)). Briefly, white blood cells were lysed in a sucrose lysis buffer, and proteinase K treated; the DNA was then extracted using phenol-chloroform/isoamylalcohol and then ethanol precipitated. Patient samples that were

received in the form of nuclei pelleted through sucrose buffer were resusupended in lysis buffer (100 mM NaCl2; 10 mM TrisHCl, pH 8; 25 mM EDTA pH 8; 0.5% sodium dodecyl sulfate; 0.1 mg/ml proteinase K) at 55°C for 4-6 hours followed by classical phenol-chloroform extraction and ethanol precipitation (Sambrook, J. et al., Molecular Cloning, A Laboratory Manual (1989)). Samples were incubated at 55°C after isolation for the inactivation of DNAse to prevent the degradation of DNA. Concentration of the isolated DNA was determined by spectrophotometric analysis at 260 nm (Sambrook et al., using GeneQuant (PharmaciaBiotech), and samples diluted with sterile distilled water to a 20 ng/µl working solution.

Primers were designed from intronic sequences flanking the exons of the hypocretin receptor-2 (*hcrtr-2*), using either primer design programs available at primer3 at the Whitehead Institute (http://www-genome.wi.mit.edu/cgi-bin/primer3.cgi) or primers for the worldwide web (http://williamstone.com/primers/javascript/). The primers are shown in Table 5.

10

Primers Used to Amplify Nucleic Acid Fragments for Analysis of Table 5 hcrtr-2 Gene

	EX-	#	Primer Sequence	Sense/	External/	SEQ
	ON	_		Antisense	Nested	ID.
5	1	1	TTTCTTCAGCTTCAGCTCTCCCTCAGC	S	E	37
	1	2	TTCAGCTCCGAAGCAGATGACCAGTTG	A	E	38
	1	3	TTCAGCTTCAGCTCTCCCTCAGCGAGG	S	N	39
	1	4	CGAAGCAGATGACCAGTTGCGACAAGG	A	N	40
	1	5	CTTTCCCACCGCAAATCACCAGTGCTC	S	Е	41
10	1	6	ATTTTATTAGAAAACCCCATCCGAGAG	A	Е	42
	1	7	TTCCCACCGCAAATCACCAGTGCTC	S	N	43
	1	8	TATTAGAAAACCCCATCCGAGAGCAG	A	N	44
	2	9	GCATGTACTTAGCATTCACACAGATTG	S	Е	45
	2	10	TCTAATGATGATTTGGCAGTTCATTGC	A	Е	46
15	2	11	TAGCATTCACACAGATTGACAGATTCA	S	N	47
	2	12	CAGTTTGTCAATGCCTTAGGCAAATAT	A	N	48
	3	13	TTTGGCAGCTTTGAATTTGCTTATATG	S	Е	49
	3	14	GCTCTTGCAAAACTGTATTCACAAATG	A	Е	50
	3	15	CAGCTTTGAATTTGCTTATATGTTGTG	S	N	51
20	3	16	TTGCAAAACTGTATTCACAAATGTCAA	A	N	52
	4	17	TCCCCTTTGCATACATAATATGACAATG	S	Е	53
	4	18	AAAAAGCACAGACAAAATATTTGGAAGG	A	Е	54
	4	19	ATGCACTTTGAAGAAAAGCATTGACATG	S	N	55
	4	20	AAGCACAGACAAAATATTTGGAAGGAAT	A	N	56
	5	21	CTCAGGCGTCTGGAAGCCTTTCCTTAC	S	Е	57
	5	22	TTAAAGGCTGTTCGCCTTACCTGCTGG	A	Е	58
	5	23	GGCGTCTGGAAGCCTTTCCTTACTGTG	S	N	59
30	5	24	CTGAGTCATCTGGCCTGACAAGGTATC	A	N	60
	6	25	GGGTCAGAAACCAATCTGTGGTCAATTC	S	E	61
	6	26	AGTTGAAGAGTGTTCATTGATTCCTCATCC	A	Е	62
	6	27	AGAAACCAATCTGTGGTCAATTCCTGCAAC	S	N	63

30

EX-	#	Primer Sequence	Sense/	External/	SEQ
ON			Antisense	Nested	ID.
6	28	TGAAGAGTGTTCATTGATTCCTCATCCTTG	A	N	64
7	29	GAGTCTACCAAGCTTCCAATAAACTCA	S	Е	65
7	30	GGATAGTTTTACTCAGGTATCCTTGTCA	Α	Е	66
7	31	CAAATCAGCAACTTTGATAACATAT	S	N	67
7	32	GTATCCTTGTCATATGAATAAATATTCTAC	A	N	68
7	33	CACTCAAATCAGCAACTTTGATAAC	S	Е	69
7	34	GTGAGAGATTAAAATAACAAGGGAT	A	Е	70
7	35	CAAATCAGCAACTTTGATAACATAT	S	N	71
7	36	TGTTTAAACATTTAATTGACACACA	Α	N	72
7	37	TTCATATGACAAGGATACCTGAGTAAA	S	Е	73
7	38	GTGAAATAGCCTGAAATAAGCTCAA	A	Е	74

5

10

15

20

25

PCR reactions were done in 20 µl reactions using 40 ng genomic DNA, 0.2 mM solution of the four dNTPs, 0.35 µM of each primer (TAGCopenhagen), 2.5 mM MgCl2 (Perkin Elmer), 1x PCR Buffer (Perkin Elmer) and 0.5 U Amplitaq gold (Perkin Elmer). The primers were used to amplify the fragments by PCR cycling at 95°C for 12 min and subsequently 30 cycles of 95°C for 30 sec, 55-62°C for 30 sec and 72°C for 1 min. The PCR products were prepared for cycle sequencing by incubation with Shrimp alkaline phosphatase (Amersham) and exonuclease I (Amersham) at 37°C for 15 min. After the inactivation of the enzymes the products were subject to cycle sequencing using BigDye Ready Reaction mix (Perkin Elmer) and subsequently run on ABI Prism 377 Automated DNA sequencers. The raw data were basecalled and sequences assembled using the Phred and Phrap software, respectively (Ewing, B. et al., Genome Res. 8:175-185 (1998); Ewing, B. and Green, P., Genome Res. 8:186-194 (1998)). The Consed viewer was used to analyze the sequences (Gordon, D. et al., Genome Res. 8(3):195-202 (1998)). Expansion of a Tstretch in the 3' untranslated region (UTR) of exon 7 of hcrtr-2 was investigated by amplifying a fragment containing the stretch with a fluorescently labelled primer

pair using the conditions described above. The PCR product was dissolved in formamide/dye solution and run on ABI Prism 377 Automated DNA sequencers as described above. Allele calling was done using TrueAllele and editing was done using DeCODE-GT (Palsson, B. et al., Genome Res. 9:1002-1012 (1999)).

PCT/US00/23021

A total of nine single nucleotide polymorphisms were identified, 7 in exons and 2 in an intronic sequence near an exon. The polymporphisms are shown in Table 6. The base number is according to the mRNA sequence (Accession number GI:6006037). For those polymorphisms marked with an asterisk (*), the polymorphism is located 5' of the corresponding exons; the numbers indicate the distance into the introns.

Table 6 Single Nucleotide Polymorphisms in *hcrtr-2*

Location	cDNA base #	Nucleic Acid Change
Exon 1	352	C-T
Exon 1	355	C-A
Intron1	-26*	C-A
Exon 5	1,170	G-A
Exon 5	1,177	C-A
Exon 5	1,201	G-A
Exon 5	1,246	G-A
Exon 5	1,266	G-A
Intron 6	-87*	G-A

20

25

15

5

10

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

-33-

CLAIMS

What is claimed is:

- Isolated nucleic acid molecule comprising the nucleic acid having SEQ ID
 NO:1.
 - 2. A DNA construct comprising the isolated nucleic acid molecule of Claim 1 operatively linked to a regulatory sequence.
 - 3. A recombinant host cell comprising the isolated nucleic acid molecule of Claim 1 operatively linked to a regulatory sequence.
- 10 4. A pharmaceutical composition comprising a nucleic acid comprising the isolated nucleic acid molecule of Claim 1.
 - 5. Isolated nucleic acid molecule comprising the nucleic acid having SEQ ID NO:1 with one or more of the nucleic acid changes shown in Table 6.
- 6. A method of diagnosing narcolepsy in an individual, comprising detecting a mutation in the gene encoding hypocretin (orexin) receptor 2, wherein the presence of the mutation in the gene is indicative of narcolepsy.
 - 7. A method of treating narcolepsy in an individual, comprising administering to the individual an isolated nucleic acid of Claim 1 in a therapeutically effective amount.

1/51

	·
LOCUS	168,575 bp DNA PRI 20-OCT-1999
DEFINITION	Human hypocretin (orexin) receptor 2 (HCRTR2) gene, complete cds.
ACCESSION	2. (12 certal) gone, complete eds.
NID	
VERSION	
KEYWORDS	
SOURCE	human.
ORGANISM	Homo sapiens
OROZHADM	
	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
REFERENCE	Eutheria; Primates; Catarrhini; Hominidae; Homo.
	1 (bases 1-168,575)
AUTHORS	
TITLE	Direct Submission
JOURNAL	Submitted () deCode Genetics, Inc., Lynghals 1,
	IS-110 Reykjavik, Iceland.
FEATURES	Location/Qualifiers
source	1 168,575
	/organism="Homo sapiens"
	/db_xref="taxon: 9606"
	/chromosome="6"
	/map="6p11-q11"
	/clone="BAC 403B19"
gene	1129,305
Ü	/partial
	/gene="HCRTR2"
	/note="OX2R"
	/db_xref="LocusID:3062"
	/db_xref="MIM:602393"
evon	
exon	20,86721,403
	/gene="HCRTR2"
CDC	/number=2
CDS	join(21,18121,403, 95,25295,430, 101,753101,996, 110,324110,439,
	124,058124,278, 127,009127,130, 128,910129,139)
	/gene="HCRTR2"
	/note="HCRTR2 exons defined by comparison to mRNA sequence (NM_001526)"
	/product="HCRTR2/orexin 2 receptor"
	/db_xref="LocusID:3062"
	/db_xref="MIM:602393"
	/protein_id="NP_001517.1"
	/db_xref="PID:g4557639"
	/db_xref="GI:4557639"
	translation="MSGTKLEDSPPCRNWSSASELNETQEPFLNPTDYDDEEFLRYLW/
	REYLHPKEYEWVLIAGYIIVFVVALIGNVLVCVAVWKNHHMRTVTNYFIVNLSLADVL
	VTITCLPATLVVDITETWFFGQSLCKVIPYLQTVSVSVSVLTLSCIALDRWYAICHPL
	MFKSTAKRARNSIVIIWIVSCIIMIPQAIVMECSTVFPGLANKTTLFTVCDERWGGEI
	YPKMYHICFFLVTYMAPLCLMVLAYLQIFRKLWCRQIPGTSSVVQRKWKPLQPVSQPR
	GPGQPTKSRMSAVAAEIKQIRARRKTARMLMVVLLVFAICYLPISILNVLKRVFGMFA
	HTEDRETVYAWFTFSHWLVYANSAANPIIYNFLSGKFREEFKAAFSCCCLGVHHRQED
	RLTRGRTSTESRKSLTTQISNFDNISKLSEQVVLTSISTLPAANGAGPLQNW"
exon	95,25295,430
	/gene="HCRTR2"
	/number=3
exon	101,753101,996
	/gene="HCRTR2"
	/number=4
	/humbol—4

FIG. 1A

2/51

exon 110,324..110,439

/gene="HCRTR2"

/number=5

exon 124,058..124,278

/gene="HCRTR2"

/number=6

exon 127,009..127,130

/gene="HCRTR2"

/number=7

exon 128,910..129,305

/gene="HCRTR2"

/number=8

BASE COUNT 55,308 a 29,672 c 29,838 g 53,757 t

CGACTTGATTTTATTTTTTGCATATGGATATCCAGTTTTCACAGCACTGCTTGTTACCCT CAGCAAAGAACAGTTGTCTGTAAATTCATGGGTTTATGTCTAGGCTCTCTGTTCTGTTCT ATTGGTCAACATATGGTCATATATCACTTAACTGCAGGGAAGGGATACATTCTGAGAAAT GCATTATTACATGATTTCATCATTGTGCAAACACTATAGAGTGTAGTTACAGAAACCTAG TATCTCTAGCTGTGTTCTTATGATTCAAATTTGCTTTTGGTCATTTGAGATCCATACTGGT GGAGTCTAATTATTCAAAACTAGGGAAAACAGACAAACAGAAAAAACTAAGACCAAGTTA CCCTTACCTTGACTAAAAAAAGAGACTCAAATAAATAAAATTGGAAATGAGACAGGAGAC ATTACAATTGATGTTAACAAAAAGATCATAAGGTACTATTATGAACAACTATACACCAAT AAATTGGACAACCTAGAAAAAAAATGGATAAATTCCTAGAAATACACAGTCTATCAAACT GAAACAAGAAGAAATAGAAAGCCTGAACATACCAGTAACAACCAAGGAGACTGAGTAAAT AATCAAAAACCTCCCAAGAAGAAGAGTCTAGGACCAGAAGTCTTCACAAATGAATTCTAC GAATATTTTCAAACTCATTTTATGAGGCCAGCATTATTCTGATACCAAAACTACGCAAAA ATACTACAAGAACATAAAAACTACAAATGTGGGAATTATCATGTATACATATGCAAAAAT CCTCAGTAAAATCCTAGCAAACTAAATTCAACAGTACATTAAAAAGATCATATAGCATGA CCAGTGAAATTTCTCCTTAGGACGCAAGGATAAGTCAACATATAAAATTGAATGTGATAT ACCACTTTAACAAAATGAAGGATAAAAATCATATGATCATCTGAATAGATGCAGAAAAAG CATATAACAAACTTTGACGTTGTTGAGAAATTGAAAGCTTTTCTCTAAGATCAAGAACAA AGCAAGGATGCCCATTCTTGCTTCTATTCAGCATAGTGCTTGAAGTCCTAGTCTGGACAA ATAAAATCCACCAAATTGGAAAGGAAGAAGTGAAATTACCTCTGTTTGTAGATGAGCTGA ATAGCTAGAGCAAAGAAATGAATTCAGTACAGTTGCAGAATGCAAAATCAGTATACAAAA AGTACTTGTAATTCTATATAATAGCAACAAACTATTTCATAAGGAAATTAAGGAAACAAT CCCCATTACAATAGCATCATAAATAATAAATCTTAAGAACAAATTTAACCAAGGAGGTGA AAGACTTGTGTACTGAAAACTATAAAATGCTGATAAAAAAATTAAAGAAGATACAATAAA TGGAAGATATTCCATGCCATGGTTTGGAAGAATTAATATTGCTAAATGTACATACTACCC AAATGAAAACACAATCTTAACACTATTTAAACCAATTAAACAAACCTATGATTTCAATTT GGTCAAATGTGTTAGAATGGATTTCCTTTTATTGTTTTGAACTTGTCTCTTCCAAATTTC AAAGCCTGGTTCCTAATTTTTACTTGAAATACCAAATAACAAACCCACTTAATGAGCTCT GAGCCAGTTTTAGTAGCCAAACTTGTATTTAAATAGTGTGTTACATATTTGCACAAAAAG CCAACGGAGTCTAAATCAACACTAATTCACATCATTACTAGCAATCTAAAACATCAGATG ATAATTTTGCTGTTGTCTTTCAGGCAAGATATTCAACCATTGGTATTAAATGTTTTATAT GAATGTGCGGTGTTTTATTTCAGAAACACTTCTCTGAATTCCCAAGGCCTAAGAGCTATT CATCATAGAGGTTTGTGGAGGCGGTAGTTAGACATTTTCTACATGCATAATGTTAATTCA TTCAAACATTATAGAAAAAAGTTTGTAAAGAAGTTAATTTTCAAGGTGACAAAAAAATC AGATTGAATCATGTTTATTTTATTTCAATTTAAACTCGTTGGCTATCTTAGGAAATTCAC ATTGTTTTTGAAGAATATATGAACAAAGTTTGATTCATCTTATCTATATAAGCATGAGAG

FIG.1B

3/51

AAATACCTAGATGAGAGTGAAAAATGACTAATTTTGTGACCATTGTTATATCATAGATTA ACTTGTTCTTCTACTTCTAAGCTGTGTGATCTTGAAAAGTCATCTAAACTTCAGGTAC CATCCTCACTTGCAAAATGAGGGGAAAAACCCCCAGCACCTTTAATATGGTGTTATGTGGA TGAAATAAGTTAATATATATAAGTGCTTAGGTTTCATGCACTTTCTATATAGTATTAAT AATATTATTGTTACATTATTATAGTTACATTATTATTTTTTATTAATATTATTGGAACATG AATGGAATTGTTGTGGCTCATTTTAAAGATGCTGCAATGGAGACCAAGAGAAATTAAGTA TAATAATCCTAGTTAAGGTACAGCCATTTCTAATTACATTTTCCAACTGCTGCTTTTACT AGAACACATAATAATCTTATTTAATTATCACAACAATTTCTGTGGAGTTACTATTAATCC AGAGATGAAGAATCTAAAACTCTAAATTATCAAGCAACTATTCCAGCTTTAAACAACAGT AAAACTGGAATTAAAACTAGAGTTTCTTTATGAGGCCAGTATTACTCTTATACTAAAGCA CAAGCACACACACACACACAGATCAATATAACTTATGGATGTTGATGCAAAAATTTT CAAAAAATTAATAGCAAATCGAATCCAGCAGTATTTTAAAGGACTATACACCATGGACAA ATGGGGTTTATTCCTGGGATATAAAGTTGGCTAAACTTAATGAAAATCAACCAGTGCAAT AAATAATAGTAATTAAAAAAACATAATTATCTCACTAGATGTACAAAAAATGACAAGATC CAACATGTTTTCAATATAAAAGCATTCCACAGACTAGGAATAGAAGGGAACTTCCTCAAC TTTACAAAGAACATCTACAACGAAACCACAGCTAACATCATATTTAATGGTGGAAGACTG AAATCTCTGAATATTTTCCCCTAAGATCAGAAAAAGACAAAGAGGTCTACTAATTCTATT CAACATTGGAAAGATAGTTCTAGTCAATTAATCATTAAAAAAAGGCATTTAGATTAGAAA GGAAGTAAAATTACCTCTGGCAGATGACATAATCTTATACATGGAGAACTCCTAGAGATT ACATACACACTCACAACTACCAGAGTTAATAAATGGGTTCTACAAAGTTGCAGGATACAA TATCAATTCTCAAAAAACACTTGTATTTCTATACACTAGCAAATAACTCTGAAAATGAAA TTACCAAGAATGTACAAGTTTTATGTACTGAAAAATAAAAAATGTCATTAAAAAATGTTA AAGAGAATCTAAGCACATTGCAGTTTTCTGACTCCAGGCCCGGGCTCTTGGATGGCATCT CTGGATCCACTCAGGACCAGGGAGAACTTGTTGCCCTGAAGGGAAGGACACAAGTCTGAC TGGCTTTACCACCTGCTGATTGTAGAAGCCTAGGGCCTTCAGGGAACACAGGTGGTAGCC AGATAGCAGTTACCATGGGCATTAGGCATGACCCAGTGCTATGTTGGCTTCTAGTTTGAC CCAGCACAGCCCAAGGGTGGTAACCACATGGGTGCTTGTGTCACCCCTCCTTAAGTTCCA GGCAGCCAGCAAAGAGAGAGTGACTCTGTTTGGGAGAAAGTAAGGGAAGAGAATAAAAGT CTCTGTTGGTAATACAAGGAATTCTTCCAGATCTTATCCAAGACCTCTATGAATCTGCAA CAGCCAAAGCATTATTAGTTTTCAGGTTTCCCCAGTGCAGATATGACTGCAATGATCAAA GCACAAACAAGTTTGGACTGGGAGGACTACAATAAATACCTAACTTCTCAATGCCCAGAA AGGAACAGCTCTGGTCTGCAGCTCCCAGTGAGATCAGTGCAGAAGGTGGTGGTTTCTGCA CAGAGGGTGAGCCAAAGCTGGATGGGGTGTCACCTCACTGGGGAAGCACAAGGGGATGGG GAACTCCCTCCCCTAGCCAACGGAATCTGTGAGGGACTGCCATGAGGGATGGTGCATTCT GGTCCAGATACTATGCTTTTCCCATGTTCTTCACAACCCTCAGGCCAGGAGATTCCCTCG GGTGCCTACACCACCAGGGCCTTGGGTTTCAAGTACAAAACTGGGTGGATCTTTGGGCAG GCACCGAGCTAGCTGCAGGAGTTATTTTTCATACCCCAGTGGTGCCTGGAATGCCAGTGA GACAGAACCATTCACTCTCGGAAAGGGAGCTGAAGCCAGGGAACCCAGTGGTCTAGCT CGGTGGATCCCACTCCCATGGAGGCCAGTAAGCTAAGATCCACTGGCTTGAAATTCTCAC TGCCAGTGCAGCAGTCTGAAGTCAACCTGGGATGCTTGAGCTTGGTGGAGAGAGGGACGT CCACCATTACTGAGGTTTGAGTAAGCAGTTTTCCCCTCACAGTGTAAACAAAGCCACTGG GAAGTTAAAGTAGGTGGAGCCCACGACAGTTCGGCAAAGCCACTATAGCCAGAATGCCTC AGCTTATAGATCAAACTCCCATCTCCCTGGGGACAGGGCACCTGGGGAAAGGGGCAGCTGT GGGTGCAGCTTCAGCAGACTTAAATATTGCCGCAAGCTGACTCTGAAGACAGCAGGGGAT CTCCCAGCACAGCGCTCGAGCTCTGCTAAGGGGCAGACTGCCTCCTCAAGTGGGTCTCTG GCAGGCAGCAATCTTTGCAGTACTGTAGCCTCTACTGGTGATACCCAGGCAAATAGGGTC TGACGTTGACCTCCAGCAAACTCCAGCAGACCTTCAGCAGACGGGCCTGAGTGTAAGAAG GAAAATTAACAAACAGAAAGGAATAGCATCAACATCAAAAAAACAAAAACAAAAACAAAA

FIG. 1C

ACAAAAACAAAAACAGCACATCCGCACAAAAACCCCATCTGAAGGTCACCAACACCAAAT ACCAAAGGTAGATAAATCCACAAAGATGGGGAAAAAACCAGCACAAAAAAGCTGAAAATTC CAAAAAACAGAATACCTCTTCTCCTCCAAAGGATCACAATTCCTCACCAGCAAGGGGACA AAACTGGACAGAGATGAGTTTGATGAATTGACAGAAGTAGGCTTGAAAAGGTGGGTAAT AAACTCCTCTGAGCTAAAGGAGCATGTTCTAACCCAATGCAAGGAAGCTAAGAACCTTGA AAAATGGTTAGAGTAATTGCTAACTAGAATAACCAGTTTAGAGAAGAGCATAAATGACCT GATGGAGCTGAAAACTATAGCACAAGAACTTCGTGCAGCATACACAGGTATCAATATCCA AATCGATCAAGCAAAGAAAAGAATATCAGAGATTGAAGATCAACTTAATGAAATAAAGTG TGAAGACCAGATTAGAGAAAAAAGAATAAAAAGGAATGAACAAAGTCTCCAAGAAATATG GGAATATGTGAAAAGACTAAACCTACATTTGATTAGTGTACCTGAAAGTGACGGGGAGAA AGGAATCAAGTTGGAAAACATTCTTCAGGATATTATCCAGGAGAACATCCACAACCTAGC AAGACAGGCCAACATTTAAATTCAGGAAATACAGAGTACATCACAAAGATACTCCTCGAG AAAAACAACCCCAAGACACATAATTGTCAGATGCACCAAGGTTGAAATACAGGAAAAAAG TTAAGGGCAGCCAGAGAGAAAGGTCGGGTTACCCACAAAGGGAAGCCCATCAGACTAACA GTGGATCTCCCTGCAGAAACCCTACAAGCCAGAAGAGAGTGAAGGCCAATATTCAACATG CTTTAAGAAAAGAATTTTCAACCCACAATTTCATATCCAGCCAAACTATGCTTCATAGTG AAGGAGAAATAAAATCCTTTACAGACAAGCAAATGCTGAGAAATTTTGTCACCACCAGGC CTGCCTTACAAGAGCTCCCGAAGGAAGCACTAAATATGAAAAGGAAAAACCAGTATCAGC CACTGCAAAAACATATGAAATTGTAAAGACCATCAACACTATGAAGAAACTGCATCAACT AATGGGCAAAATAACCAGCTAGCATTATAATGACAGGATCAAATTCACACATAACGATAT TAACCTTAAATGTAATAGGCTAACTGCCCCAATTAAGAGACACAGACTGGCAAATTGGAT AGAGAGTCAAGACCCAACAGTGTGCTGTATTCAGGAGTCCAATTCATGTGCAAAGATACA TATAGGCTCGAAATAAAGGGATGGAGGAATATTTACTAAGCAAATGGAAAGCAAAATAAA GCGGAGGTTGCAATCCTAGTCTCTGATAAAATAGACTTCAAACCAACAAGATCAAAAGA CTATAGAGACTTAGACTCCCACGTAATAATAGTGGGAGACTTTAACACCCCACTGTCAAT ATTAAACAGATCAATGAGACAGAAAATTAACAAGTACATTCAGGACTTGAACTCAGCTCT ATTATTCTCAGCACCACATTGCACTTATTCTAAAATTGACCACATCATTGGAAGTAAAAG AATCAAATAAGAGCTCTGGAATAAGAAACTCACTCAAAACCGCACAACTACATGGAAACT GTTACTTGAAACCAATGAGAACAAAGACACAACATACCAGAATCTCTGGGACACAGCTAA AGTAGTGTTTGGAGGGAAATTCATAGCACTAAATGCCCACACGAGAAAGTGGGAAAGATC ATAGATAGATCACTAGCCAGACTAATGAAGAAGAAAAGAGAGAAGAATTGTATAGACACA ATAAAAAATGATAAAGGGGAGATCATCACTGATCCCACAGAAATACAAACTACCATCAGA GAATACTATAGACACCTCTATGCAAATAAACTAGAAAACCTAGAAGAAATGGATAAATTC CTGGACACATACACCTTCCCAAGACTAAACCAGGAAGAAGTCAAATCCCTGAACAGACCA ATAACAAGTCCTGAAATTGAGGCAGTAATTAATAGCGTTCCAATGAAAAAAAGCCCAGGA CCAGATGGATTCACAGCCAAATTCTACAAGAGGTACAAATCAGAGCTGGTACCATTCCTT CTGAAACTATTCCAAACAACAGAAAAAGAAGACTCCTCCCTAACTCATTTTATGAGGCT GGCATCATCCTGATACCAAAACCTGGCAGAGACATACACACAAAAAAAGAAAATTTCAGGC TAATATATCCCTGATTAACACCGACGCAAAAATCCTCAATAAAATACTGGCAAACCAAAT CCAGCAGCACATCAAAAAGCTTATCCACCACGATCAAGTTGGCTTCATACCTGGCATGCA AGGCTTGTTCAACATACGAAAATCAATAAATGTAATTCATCACAAAAACAGAACCAATGA CAAAAACCACATGATTATCTCAATAGATGCAGAAAAGGCCTTCAACAAAATTTAACAGCC CTTCATGCTAAAAACTCTCAATAAGCTAGGTATCGATGCAATGTATTTTAAAACAATAAG AGCTATTTATGACAAACCCATACCCAATATCATACTGAATGGGCAAAAGCTGGAAGCATT CCCTTTAAAAACTGGCACAAGACAAGGATGCCCTCTCTCACCACTCCTATTCAACATAGT GTTGGAAGTTCTGGCCAGGGCAATCAGGCAAGAAAAAAATAGAAGGTATTCAAATAGG AAGAGAAGAAGTCAAATTGTCTCTGTTTGTGGATGACATCATTGTATATTTAGAAAACCC CATTGTCTCAGCCCAAAATCTCCTTAAGCTGATAAGCAACTTCAGCAAAGTCTCAGGATA CAAAATCAATGTGCAAAAATCACAAGCATTTCTATACACTAATAATAGACAAACAGAGAG

FIG. 1D

CCAAATCATGAGTGAACTCCCATTCAAAATACCTAGGAATACAACTTACAAGGGATGTGA ATGCAAAAACATTCCATCCTCATGGATAGGAAGAATCAATATCATGACAATGGCCATACT GCCCAAAATAATTTATAGACTCAATGCTATGTTCATCAAGCTACCACCGAATTTCTTCAC AGAATTAGTAAAAAACTGGCCAGGCTCAGTGGCTCACGCTTGTAATCCAAGCACTTTGGG AGGCCAAGGCAGGAGCTCAAGAGGTCAGGAGATTGAGACCATGGTGAAACCCCGTCTCT ACTAAAAATACAAAAATTAGCCGGGCGTGGTGGCAGGCGCCTGTAGTCCCAGCTACTTG GAGAGGCTGAGGCAGGAGATGGCGTGAACCCAGGAGACGGAGCTTGCAATGAGCCAAGA ACAAACAACAAAAAAAAAAAACTACCTTAAATTTCTTATGGAACTAAAAAAAGAGCCCAT ATAGCCAAAACAATCCTAAGCAAAAAGAACATAGCTGGAGGCATCATGCTACCTAACTTC AAATTATGCTACAAGGCTACAGTAACCAAAACAGCATGGTATTGGTATGAAAACAGATAT ATAGACCAATGGAACAGAACAGAGGCCTCAGAAATAACCCCAGACATCTACAACTCTCTG ATTTTTGACAAACCTGACAAAAACAAGCAATGGGGAAAGGATTTCCTATTTAATAAATGT TGTTGCGAAAACTGGCTAGCCATATGCAGAAAACTGAAACGGGACTCCTCCCTTACACCT TATACAAAAATTAACTCAAGATGGATTAAAGACTTAAACGTAAGACCTAAAAACCATAAG AACCCTAGAAGAAAACCTAGGAAATACCATTCAGGCCATAGGCCATGGGCAAACACTTCAT GTCTAAAACATCAAAAGCAATGGCAAGAAAATCCCAAATTGACAAATGGGATCTAATTAA ACTAAAGAGCTTCTGCACAGCAAAAGAAACTATCATCAGAGTGAACAGGCAACCTATAAA ATGGGAGAAAATTTTTGCAATCTGTCCATCTGATAAAGGGCTAATATCCAGAATCTACAA TGAACTCCAACAATTTACAAGAAAAAAACAACCCCATCAAAAAGTGGGTGAAGGATGTG TCATCACTGGTCATTGGAGAAATGCAAATAAAAACCACAGTGAGATACCATCTCACTCCA GTTAGAATGGCGATCATTAAAAAGTCAGGAAACAACAGATGCTGGAGAGGATGTGGAGAA ATAGGAACGCTTTTACACTGTTGGTGGGAGTGTAAATTAGTTCAACCATTGTGGAAGACA GTGTGGTGATTCCTCAAGGATCTAGAACCAGAAATACCATTTGACCTAGCAATCCCATTA CTGGGCATATACCCAAAGGATTATAAATCATTCTATGATAAACACACATGCACATGTATG ATAGACTAGATTAAGAAAATGTGGCACATATACACCATGAAATACTATGCAGCCATAAAA AAGGATGAGTTCATGTCCTTTGCAGTGACATGAATGAAGCTGGAAACCATCATTCTCAGC ACAATGAGAACACATGGACACAGGGGGGGGGGGGAACATCACACACCAGGGCCTGTCAGGCAGT GGGGGGCTAGGGGAGGATAACATTAGGAGAAATACATAATGTAGGTGACAGGTTGATGG GTGCAGCAAACCACCGTGGCACATGTATACCTATGTAACAAACCTGCACGTTCTGCACAT GTATCCCAGAACTTAAAGTATTAAAAAAAAAAAGACCATTTATGAAAACATGACCTTACCA AAGAACTATATAAGTCACTGGAGACCAATCCTGGAGTGACAGAAATATGTGACCTCTCAG ATGGAGAATTCAAAATAGCTGTTGTGAGGAAATTCAACAAAATTCAAGATGACATGGCAA AGGAATTCAGACTTCTATCAGATAAATTCAAAAAAGAAGATGAAATAATTTTTTTAAAAA TTCATGCAGAAATTTTGGAGCTGAAAAATTCAATTGATATACAAAAGAATGCATCTTACC AGCAGAATTGATCCTGCAGAAGAAAGAATTAGTAAATTTGAAAACACTCTATTTGAAAAT ATACAGTCAGAGGAGACAAAAGAAGAAAATTAAAAACAATGAAGCATACCTACAGGATCT AGAGAGAGAGTGGGATAGGGGTAGAAAGTTTATTCAAAGGGATAACAATAGAGTATCAGT ATTCAAATACAAGGTTATGGAACACCATTCAGATTTAACCCAAAGAAGACTACCTCAAGA CATTTAATAACTGAACTCTCATTCAATGGGAAAAGTAAAGTCCTTTCAATAAAGGTGTTG GGATAATTGGGTATGCAAAAATGAATTTGGATACCTTTCTTGTGTCATATACATAAAAC CACAGTAAATTTTTGTGACCTTTGATTAGGCAATGATTTCTTAAATATGATAAAATATGG TAAAAGCAACAAAAGAAAACATGAATAAATTGGATCTTATCAAAATTTAAAAACTTTTTTG CATCGTAGAATACTATCAAGAGTATGAAAAAGAAAACCTACAAAATAGGAGAACATGTTTG TATATATATATATATATATACTCTTACACCTCAACTATAAAGAGACGAATAACCCAAT AAGTTCATCAAAAGATGCTCATCATCTTACTCAGGAGGCAAATACAGATTAATATTACA ATGATATTAGACATGGATTTGTCATATACAGACTTTATTAAGTTAGATTCCCTCTATGCC TAATTTGTTGAGAGTTTTTATCATGAAGAGATGTTGCATTTTGTCAAATGCCTTTTCTGT GTCTTTTGAGATGATCATATGGTTTTCGTCCTTTATTTTGCTGATATGATGTACCACATT

FIG. 1E

WO 01/30991

6/51

TATTGATTTGCATTTATTGAATCATCCTTCCACCCCTGGGATAAATCCCACTTGATCATG GTGTATTATCTTTTGATGTTTTTTGGATTCACTTTGCTGATATTTTGTTGAGGATTTCT GCATCTATAATCATTAAGGATATTGGCCTGTAGTTTTTCTGTTTTTTATGTTGTATTCTAGT CTGATTTTGGTATCAGGGTAATGCTGTTCTTGTTGAGCGTGTCAGGAAGTCCAAAAGACT TAGAATTCAGCAGTAAAGCCATCCAGTTCTGGGCTTTTCTTTGTTAAGAGACTTAAAACA CACACAACGCACACAAAATGAAATATCACTTTCCACCCATTATAATTTACAAAGTGGA AAATAACTCGTGTTGATAAGAATGTGGAAACCTTGAAACCTTCATGCATTGCCAGTGGTA ATGTGAAAGAATCTTGCCATTGTGGAAAACAATTTGTCAGTTCCTCAAACAGTTCAACAT AGAGTTACTGTATGAAATAATTCAACTCCCAGGCATGCACCCAAGAGCATTGAAAACATA ATGGAAACAATCCAAATATTCATCAACTGCTGAATAGATAAAATGTGGCATATCCATATA ATTAAATACTATTCAGCCACAAAAATAATAAAGTACGGATAGACACTAAAACATGGAAGA ACCTTGAAAATATTAAGCTAAGTGAAAGACATAAGACACAAAACCCAACATTTAAAGGAA ATTTCCAGAATTGTCAGATCCACTGAAGAAGAAACTTGAGTGTTTGCCAGCATGTGGGAG GAGAGGAAAATCAGTAGTTATGAGGTTTCTGGAATTAGTAGTGCTGATGGTGACACAACA TTGTGAATATACTATAAACCACTAAATGATACCTCTCAAAATGGTTAAAACATTACTGTT GTGTTATGTGAATTTACCTCAATTAGAAAAGAAAAAATCTTATCAATAACAAAGAGAA ATTTCCACACAGGTGGGATCGCTTCCACAGTGCTACTCAATGCAGTTTAGCGATTGCAT TTGTATTGGAGTAAAAGCATGTCACATTGCTTTTAACATTGGAGTCCAATACATAAACCT AATTTCACAACACAATGGATCATTTTTTTTTTTCATGTGGAAAATCAGAACACATGCCTTA ATGGTTACATGCCCCACCTGCTGCTCACCTAAAAGTAAATTTCCTCTAACTCAGACAAAT ATGTTATTTCAAGGAAAAGAAGCCCAGAGAACTGAGATCCAGAAGAAATAACATGTATT GAAAGCACACAGAAGTATTTCAATGAACTCAAACCCAAGATTGTAGAAAACTCTCATGTG CCCACCCTTCAGAGCACCCGACGATAATGGATAGTTTCTAGCAGGGTGTCTGGAATGGGC AAGTACCCCCAAAGTTATAGTTTGTACTGCAAGACTTGAACCCACTCTTTTTCTGCCCTC TATTATTATTTTGCATTTTAACCATTTATTATTTTGAAAAGAAAAGAGAATTTTTAGAA TATGGAAAGAGGAAGTGAATTAATAAAATAGCACACCCTACATAGAGACTGCTAATCCAT CTCCAGTCTAAAGATTTAGTAATAGGCAAGAATATACATATCCAGGAATTTCCTTGGTGT TACATAAACAAAGGCGGCACATATGTATATTTTTCACAAAATATTCACTGTTTGAAGAAG GAATTACTCCCTTCAATTGAGTTCAGGCCTGATCAACAAGTAGTGATTGGCCAACAGCTA GGAGATGTCATCCTGAAGAGTATAACAAGTTCCCCTATAATTCTACTTTTCAGTACTGTT TAAAATACAACTGGATTTTTTTAAATATGTAAAATTTATATAATTTTACAAATGTCTTTG TTAAGAATTAAAACTATCATTAGTAAAGGACACAGCTGGAAAATTGAAAACATTTTGGTT CTCTACTGTGGAAACAGAATAGAGTAACAGCAAAAAGCGTATTTCTGGAATTGGACCCTG ACAACTCTGCTTAAACACTCCACCACTTTCTAGCTATATGACCTTGGGTAAGTTACTTAA CTTCTTTGTGTGTCAGTTTCTTCATTTGTAAAATTGGAATAATAGATGCTTTTTTTGAGA CAGTGTCTCATTCTGTTGCCCAGGCTGGAGTGCAGTGGCGTGACCACAGCTCACTGCAGC CTCAACCTCCTGAGTTCAAGTGATTCTCCAACTTGAGCCTCCCAGATAGCTAGGACCACA GACACATGCCACCATGCCTGGGTAATTTTTTTTTTAAGTTTTTCATAGAAATAGTGTCTC ACTAAGTTGCCCAACCTGGAAAATTGGAATAATAATTCATAAAATCTTCCTCCTAGATTT GTGAAGATCAATTGAGTTAATGTATGTAACGTACTTGGCACAGAGCTTGGCCCATGTAAT CAATGTCTTTTCCATATGGTTTCATTGACGCCACTTTGGGAAAATAGATGTCTCTTCTGC TTGCATTTTCAGACCTTTTTAGGTGTATACCTTAGGGCATTTGCTTTACTGACCAAAATT ATTTGCCGGCTACTCTGTGCTTTTCATGACACACTGAATAAGACAGGAAGAGTGTTTATC TATGCTCAACATAAGATAGGCATATAATGGAAGCTTCGTATATATTTGTTGAATAAAAAA CATAAGGGGAAAATATCAGATCTAATAATGCAGGACAGGAGGCAAGATGGAACGGAGAGA ACCTTGTCTGAGAAGAGACATAATTAAAACAGGGCATGGGAGGTAATAGAAAGATTGGAG GAAAAAGAGACAGAGACAGAAATGTTTGTGGTAATTTGTGACAAGTAGCTTTGATTGT TCATGGCCTAATCTTTTAGGGCATGAGGTTATTTCATTCTCTGTAGCCCACCGAGAGTGC GTACAGTGACACATGTTATGTAAGTCCCCTTTTCCCTTTTTATAAATGTCTAGACCCCCT

FIG. 1F

7/51

GTGATTTGAGACTTTTCTAGAAGAATTTAGCTGAAGACCATATTGTTTTTTAAATGTAGT ATATAAGCTCAGTATCATCATTACCAACAGTGCTCAGACTTGATTTTATTTTCATTCCAA CAGCAAAGGAAAGAAAGCAACTTCTTTCATGCTTCCATGCCACTCTGCATCTCTACCT TCACAGAGTTTCTCAATAATGGCAACATTTCCAGTTCACCAATGGACTGAGAGATCATTG AGGCTAGACTAGTCTTATTAATCCTTATACCCCAGCTCCTAGCCGAACTCCTGGACACAC AATAGATACTCAGATACATTTACTGAAATGCATATAGAAAGTTACACCTGCAAAAAAAGAT GATCTCTCACCAGGAATAAGAAAATATAATCTGGGACAGCCCATATATGAGATCTCTAAA $\verb|CTAGGTATTTAAACAGAATTATTCTGAATGTTGTGAGCTACATTTCTTTTTTACCTTTTA|\\$ CATAGTATTTGTATATATTTATAGGGTACATGTAATATTTTGTTACACGCATAGAATGTG GCTAGGAGCATGTTAAGTCCTCTTTTTAGCTATTTTGAAATGTACATTGATGTTAACTA TCATTAACACAGAGTAATTGATATGTATAGCAAATAATATTTGCAGTAGGATATCACATG TTTACTTATTTATTTATTTATTTATTTATTATATACTTTAAGTTCTAGGGTACATGTGCA CAACGTGCAGGTTTGTTACATATGTATGCATGCGCCATGTTGGTGTGCTGCACCCATTAA ACAGGTTCCAGTGTGTGTGTTCCCCTTCCTGTGTCCAGGTGTTCTCATTGTTTAATTCC CACCTATGAGTGAGAACATACGGTGTTTTGGTTTTTTGTCCTTGCGATAGTTTGCTGAGAA TCATGGTTTCCAGCTTCATCCATGTCTCTGCAAAGGACATGAACTCATCCTTTTTTTGGC TGCATAGTATTCCATGGTGTATATGTGCCATATTTTCTTAATCCAGTCTATCATTGTTGG ACATTTGGGTTGGTTCCAAGTCTTTGCTATTGTGAATAGTGCCGCAATAAACATATGTGT GCATGTGTCTTTATAGCAGCATGATTTATAATCCTTTGTGTATATACCCAGTAATGGGAT GGCTGGGTCAAATGGTATTTCTAGTTCTAGATCCTTGAGGAATTGCCACACTCTCTTCCA CAATGATTGAACTAGTTTACACTCCCACCAACAGTGCAAAAGTGTTCCTATTTCTCCACA TCCTCTCCAGCACCTGTTGTTTCCTGACTTTTTAATGATCGCCATTCTAACTGGAGTGAG GCACTGGTCTGAAAATATCAATTCATTTAATTCTTTTAACAACCTTAAGGGGATATCATG CAGCAGAAATATTTGAATTGAAGAGAAGAGTAATACCTAAGAACTAGAAATTCCTTTCTT ATGTTTCAAAAGATATCAAAAGATCTAAGGAAGATATTCACATCAAAAATGAGTATTATA ATATTTATTATCTATGGTGCACTTGCAAAAAAGAAAACAAGTAATAATCTGAAGATTTAA GTGAATATTTTATGACATTGGAGTACCACATATTTAGAAGAAAGCACCAGAGAAATCATA GATAGAAGGAAATGGAATATTTGTAGGATCAAGATAAATACAGCTTGTCATAAAATAAAG ACTGTGATGATTAATTGTAGGTGGAAGATTTACGAAGAGAAGACTGAAGTATAGACAAGT TGAAGTGCCACAAAATGAAAGCTAATGACACTGACTACTTAGGAAATAGCAGACTGGGTC CATATTTATAGATTGTCAATGACAAGGAATTTGCAGATGTTAATGAATATAGATCCGAAC TTAAGTTGCAACAACCTTTCCCACTTTGAGATGAATAGTGCATGGAAGAGTAAAATGCAG ATGTTAATAAATCAGAGGAAGACATCGTGCCAGAGTATAAAGTTGACAGATTTATGCCGA TGAACTTGAACAAGCCACAGAAGGCCTACTTGTCAAATTTACTGGTGACAACAGGTCTG GAGAAATGGCTAATGTTTTGGATAATAGCATTAGAATTTAAGGTCTGTTTAAACTTCAAA TTAACAGAATGAAATTAATATATGCACATATCAATTGGGTCTTTTGCTTATATATCATCT CTTAATAGAGCCTTTTTGAACAATCATTTCTAATGTGACCTTTGGGATTTTCTACTCATC ATCACCTCATCCTGTTTGGTTTGCATTATAGCATCTATCCCTTCCTAACGTTTTCCCTAT GTATTTGTTAGTTTGTTTTTTTTTTAATCTAACTTTACTAGAAAGTAAAATGCATGGAAAC AGCAACCTGTTTAACTTTGTATCACTAAGAGTGGAAAAATAACCCTCAGGAAATATTTGG TAAAATAATAAAATGCCCATTGATGCCCTTCTCTTAAAAAGAAATTTAATTAGTGCAGAT TGGGGAAATACAACAATATTTCTCATAAAATGTGATATCTATACAATAACAGAAGTACTA TGTCCCAAAAAGTATTCTATAAATAGAAGAAGAACAGATGGTTTTGCTGCTGATTAATC CATTTATCTTTCGTAAATCATCTAATTTCCCCAGGAACAGCTTCCTCATCTATTAAAGGG GGTTAGTAATAGCTAAGCCCTCAGGGGTTTAAAAATGCATATGAAATAATTTTATAAACC ATAAAGCACAAAACAAATATGAAAAATTATGATTGGAGGAGGGGGTGGGGTAGTTAACTA AATCTCAGTGTAAACCACCAATGTCTTGTGTGTGTTGAAAAAATAATTACATATAAAAAC TGGTTGCATCCAAAGAATAATGTACTTTTTGCACTGGCAAGACTCAAACCATATTATTGT

FIG. 1G

TACTTCCTCCCAGTTACATATTTTGCAAGATATTGACAATTGTCTAAAGGAAGACCAAAC AGATGTAGGTGGGAGCTACTGTCATTTGAACAACATTGAAAAGAAAAATACTAAAAAAGA AACATGAGGGCATATAAAGGAGCGCTGGGGCTGTGATGTTTATTTTGAATCTGTGAAGCA TTGTCATGTGGAAGATTTATTCTGTGTAGCACCAAGATGCAAACTAGGAATTAGAGGTAA AAGTCTCAAAAAGACAAATCGTGGCTTGAGACCTTGGTTTAATGTAAGAAACAGTTTTCT CACCCTTAGAGCACTCCCATAAGGATGGAAGTAGTGAATTGTGGTGGTCACATTCAAGCT AGATGGGGACATGTCAGCAATGTTATCAGGAGGCTTCTACTCTGAAGCTGAAGTTCAGAC AAGATTTCCAGGCTCTTCCCAAGTGCAAGATTGTAATTACTTAAATGCAATATTTTTACC ATGTTTATTAAGAATAAAAGGATCATGAATTCACATTCTGACAAATGCTAGAATACTTAT TATTAGAGACAAAACCAGTGCATGAGAGAATGGCAGGTGACATCAGCCCTGAATCAATGG CATCCTACAGTGAATGTTTAATATCATTGAGTATATTGGTGGTCTGTCATGCTTGACAAC ATTAACTATGATCATATTTATGACACTTGGCGTCCTTCAAGAATTTGTAGCTCTATTTCA CATGACACTTAACTATCGCAAATACAAATTCCAGCTAAATAGACCCTTCAGTTTAAAAAC AGTCTCATTCTCAAATTTTAAGGAGAAAGTGAAGACGGAGATGTCTTAAAGACTCGGCAA GTACTAAGTTGGCAAATGTCAAATGTTAAAATAAGTTTTATATTAAATGTTAAAGTGTTTG CCTGGAATGACTTTTCCATTGTCCTGCTTGAGAAACACAGAGGCACCTCCTTATTGCTTT TATATTTGCTTTACAAAGACAAATGTATCAACATGCTCTGTATTAATTGTATGTTGACAT TTTTGTCATATCCACAGACTGATGCATGTCTGTGCATGGTTTATAATAAGTGCACGTAAA AATAGAGAAAATAAGTAGAAAAAGAGAGAGATTTAACTCTCACCCCCACCCCCAAAAA AACAGATTAAATTAGTTTTCATTACTTTTTTTTTTTTTCTTCAGCCTCAGCTCCCCTCAG CTAGTTCCTCAGCTGCCTATCTTCCCGGTGCAACATCGCCTGTAAAGACAGCAAAGCCAC CGCAGAAGTTGCCCGGCAGAAGACTCCGGAGGCATTGGCTCAGTAACTTTTCACGTCATT TTCTGCTCGGGAGCCCTTCTAGCCTCTCCGCGCAGCCTTTCCCACCGCAAATCACCAGT GCTCATGGGGCAGGCGGAGGGAGCTTGCAGCATTGAGCCGGAACCGGACTTGAGCCCGTG ATGTCCGGCACCAAATTGGAGGACTCCCCCCTTGTCGCAACTGGTCATCTGCTTCGGAG CTGAATGAAACTCAAGAGCCCTTTTTAAACCCCACCGACTATGACGACGAGGAATTCCTG CGGTACCTGTGGAGGGAATACCTGCACCCGAAAGAATATGAGTGGGTCCTGATCGCCGGG TACATCATCGTGTTCGTCGTGGCTCTCATTGGGAACGTCCTGGGTGAGTCTCCTCCCGGG CAGCCCTCCTAGGGGCTATCACCCCCTCTCCGCCCCGGGCTGAGAAGGCTCTAAAGAGAC CCCTCCCTCCCCGGGAAGCAAACAAAGAGGTCGCTGCTCTCGGATGGGGTTTTCTAATA AAATAATAATAATAGAAAGTTTTCTGATTTTCCGAACCGGGACCGAGCCCTGGAAAG GTTATTCCCTGTTTTGCAGGAATAACGGGGAAACCGCGTTTCTTTTCGAGCACCTAGAT TACAAGCGCAGGGAGAGGGGCCGCGGCAGGGATCTCCAGGTGGATTTTGTTGAGTGTGTG TGTGTGTGGGTGGGTGGGGGGGGGTCAGTCATCCCTTTGTGTAACGTGGCTGGGTGTT TCAGGGGGGTTGGGACGAGACAGAGCTTGCAGAATACAAAGCTACATCCCTAAGGAGCAA GCTCTCTGTGGCTGTGGAAGTCACAAAGCATTTGTGAGCTAGGTGGCATTGCCCTTTGGC GAGGAGGTTTAGTCTCCAGTCAAGAGGTGGTAATGAACCAGCAGGAGTGGAGACGGAGG CAAAGCAGGGAAGTGCACTCACTCATAGAAGCTGAATTAAACAGGATCCATGCCTGGAGC ATTCTTACATCCATTCAGCCAAATATTTTTTTTTTTTCAGTCTGCTTGTTGCCAGGCTCAG GACTAAGCTTAATGCTAGGCTATTTGTCCCGGTCTAGGTCTGTATGCAAACACGGGTTTC CTCGACCCCTCATCCCCCTCCCCCTAAACAATTTCTGAGGGTTGGGGAGGGGTGAGATG GCAACATGGTGAGTGCGATGATGGAATGTATTAGGGCAGTTGGGGAATATACCTCCAGAA AAGGGGCTTTGGAAGGGAGGGATAACTTGAAATAAATTGTGAATGGAAGGAGAGTGTACC TTGATGAATGAAGAGTAGAAGGCTGGGAGACTTTTCACATGCAGAGGGCAGTGTGGAGGA AGTCTCTGCTGAAAATGACAGGAGATGGAGGAGGCTAGGAGTTGCTCTTGATTTTCATTT ATAAAAGAAGAAGAAGGTGAGTGAGATAGGCTGGGAGGCTTTGCAGTCAAAAGCA AAGAACTTGTAGCTGCAATGGGGACTGACAAGGAAATTATCAGGCTTTCAGACTAACCTG ATTTTTGCCTTCTCCCAAGTGTGTTGGTCTGGGTAGAAATCATCCCGAGTAGTCTCTC ACCAACTCAGCAGGCAGAATAGATGATAGTATGTGAATGACAGGAGTTCTCCAGAGTGTT GGTAGAATGTTATTTGAGGAGACAAGAAACCTCTGAGAACTTTAGTACATTTTTAAATAT TATTTTTAGACTGTTTTCCTTTGGTTGATTTAAAAGTAAAAATAAAGGAAATCTTTTTGG GATACTAACAAAATGAAACAAAAGTGGAAATACACAAGATTAGGATTCTTGTTATAAGCA

FIG. 1H

TAATTCTGTTGATAATAATCCTAATCTTGCTTTCCTTCTTGTTACCCATCCTTAGGA TTACATCTCTTAAGACACATGGCTACCAGCATAGCAACATTTTACTGCATTATGCCAACA CTTATTGATAAGTGAATAATCAAAATTGAACATATATTGAGTACCTACTGTGTGCCAGAG CCCTTCATGTACATTCTCTCCCTTAAATATCAAAATAACCCACATTAGCCAGAAGAAGAA ACAAGACTTAGAGAAATAAAATGACGTATTAAGGGACATAATTTAAATTCAGTTCCATTT TTTCTGACCTCAGATCCAGAATTCTCCATTGTTATTCCACTCTAGAGCTAAAAAGCATAT AGAGAATAGATTCTCTGCTCCTGATTGTCTGCAAGTTTATTAGATGTGTTCCTGTTCTCC TCTGCATCAACGCCCACTGCCAATAAAGTACAATGAGGGATTAATGGCACTGTCATTCTC TATTTGCCTTCCTTATTTTAATTTTCGGCTGAATCTTTGTGGTAAAATGTGCTCTTCTTT GTTGTTATTGCATTTTACCTTGCATAGACCTTGTAGTGAATAGTCTCCATATCCTAATT GCATAGTTTAGGGATACATGTTTGCTAGCCTGGGGAGTTTTAGTTTCAAGAAGGAAACAC CTCTACAGTAAGGCTACTTGTTTCATAATGTCAAGGAAGATAGCACTGTCCACAGCCCCA CTTAAAGAAACTGACAGCTATTTTCCTCAGGACTGAATAACACTGAAATCCTCTGGTT GAACTGAAATGCATTCTTTTCTGACATACTGCCTGAAAGTTGATGAGGTTTAGGTTTGAC ATTTAAACAAACGAGTAGTGTCGTTACTCACAGACAACTTCCTGCTCTTTGATGTCACTG TCAAATTTGCAAAATGAATTAGATTGAGAATTGCTTCTTTGCCCCTCTGGTATAAGTAAT TTTGCACATAGAGTGGTAGGACAGGATGTCACATGATTTATGCAAAATAAAGATGCAATA TTAAGTATGAAGGTAAAATACCACAGTGTAGGCAGCAGATGTAATCACTGAGCCTTCAGG TCCAGTCACCATTTGTACTTTCATATAACTGCTTGGAAAATCTCAACCTTTTTGGGCTTA CAAATATAATGCCATCAGTTAGAAGTCATCTTCTCCACAATGTCCTTTCATGAAGTGATG TAATAGGATATGCTGTGGGTAGCATAACAAAGTCTTGATTGTCCTCATCTCTTTTTCTTC TCCCCATAGTCCCTCTTTATCACTATGCCACCTCTCCACTCTCATATACTCCTCCCAAAG ATGGAAAGCAGTTTCCTGGGGGAGTAAAGTTTTAAATAGAATGTTATGAGTATTTACATT GTAAGGTTCTTTTGGAAGGAGTATCTTTTCAGTATCTTCAGAATAATGCCACCTATAAC CTATTCCTAACTATGTCTTCTACTACAGCTAAGTAGATGTATCAACTTATTCAATTGGTA TATTGTGAGCATTATCATTTTTTTAAATTAGTGTGTATATCAGGGGAGCCTCTGGGGAAA TGTAAAGAAATGTGACTGATGTTAATTTTTACTCCTGATTCCTTGAATGACAATTGTAGG GAGAAATGTGTTCTAGTCAGTTTAAACATTAAGTACCTAGGGAAAATGATCAATTTTCTG CTTCTCATATCTGCATTCAAAGATATCATATGTTTCATCTGGTATGCTTCTGTCATATCT GTTGTTGTCTCCATATGGAAAATAGGAAAACATCAGTCTAGCTATGCTTCTTGCTTCTTG TGTGCCATTAGCAAGTTATTGAACTATCCAAGTCAATTTTTTTATAATTACAAATTAAAG ATCGATAATGACTGCATTATAGAAATAGTATCAGGATATAATGTACGTATACCCTCTATA AAGACATATAAAGGGACACAGGCATATACATATTTTTCTTGACACATAGACACTAATTAA TGTCAATTTTTATCCCTTAATTTTCATGACTGAACTTTTTGTGATGTGGTGTATAGCCAG CTTCTGCCTTCATGGGCCAGTCTGTATCTCTGTAGCTCTTTATGGCCTCTGCCCCAGCCT TTTCCTTAATTGCATATTTTCCTAAAAGGTGTGAATAAAATGGTGTTGGCACACATTACT CTCCTTTTCCACACTAGCTCCACCCACCCATCTCCTTCATACTGATTGCTTAACATTGCC TTCTTGCCTTTAAATGAAAGCCATTCCTAACTATTGGAATAGTTTGCTTTCTCTCAAC TTAAATTTGCCTGTGCTGGGTCCCATTCATTTAGAGTTTTTGAGTTGTTAATAGGTTGTT TAAGTAATTTACCTAATAACAGTTTACCCAAGTTAGGTGTGTGGGAATGGGGAAATATTTG TAATAAGTTTGCTTCCTACAGAGTTAGTCTTGTGTCAGATATGTAAGTGGTAGAATTGCA AGTTCATGTTACTCCTAAGCCTAGAGACATTTATTTTCTGCTTCTCCGAATGCCCATTTT AGTTTCATGGGTGTTTGTAAACCCATCCTTACCTACACAGGAAGCAAAAAGGGGTTATTT CTAAACCCTTTTTAGATATAGAAATAATACATCACTCATCTCGGCCAAGACTCAATAGAA TCATGAATAGTGACTGTAAAAGGTAATATTAACTATTAGGCTTTAAACCTATTGTGCATT TTAGTTTTAAAATGCAAACATGCTAATCTGAATAAGAATTAATCTGATGCCTCTACATTT ATCCCAATGATAACTTTTAAGATGGCTATTTCATAGATAACAGCAACATTTATCATGGAC AGACAATAATGAGAATAACATGTGCAACTGATAATTTAAATGCAATGAGTTATTTCTGTA TTTGAAAAAATATATTTGGGAAATGGGATAATTAAAAAATACCAGTTTTCAAGAGACCAA ATCTAAAACTCAAACATAAACACAATGCTCCAGTTTTTAGAAAACTGTCTTGATTGTAGT AGTGCCTACATACTAAATTGTATCATATGATTTATATTAATTTTCCTTATTTTGTATTTT

FIG. 1I

10/51

AGATTATATTTGAAAATTTTCATGTACTGCAGCTATGTTAGCATCTCAAAGTCTCCATAT TCTCACTCCGCTCCGAAACATCCACTGCTGATGTTATTTAACTAGTGAAAGAAGATCCTT CCATGTTTCTTATAGCATTCTGACATCTTCTCCACCCTAAGGAATGCTGGCTTTATT AAGTATGTTTCAGTCAATGACATGTGATTGGTGAAGCTGACGGTATTTGTCTTCAGTTCC TTTTTTCCCTGCAAAGGAAATTTGTTGAATATTTATTGGGTACTATATGCCAGGTACTAT ATGTCAGGCTCCACTTACATATACTCTATTGATGCCTTACAACAAACTTATAATGAGAAG ATTAATAGGTTTTACAAATAAGAAAAATGAATTCAAAGAGCAATGCTAACTTACTCAAAA GTTTAGTCAGGCAGTAAATAGCAGCACTAGGTTTCAAATATGGATTTAACAAATTCCATG GTCCATGCTTATTCCATTACTTCATCCTGCCTCTTTCCTTAGCTTCTAACCCTGACTGGA GATGCATAGGCAAAAAGAGGAAGGAAGAGATACTTAGATGTGCCCTCTAGACAATTTACA GAGTTGTTTGGGCATGTTGCCATGCTGTTTTTCTGATAGACTACAGTTCTTCAGCTCTGA GGATGAGCTCATTTGATAAGCCAATCAAGGTCGGGCTAGGGTTACTTTACAAGAGAAAAT TTCAAGGTAAAATAGGTGCTGCCAAAAATGCTTTTACCTGTTCAGGGGGTTGACTCACTG GAAAAAAATGTTAGATAATTGTGGCCAAGGATTATTTTGTTATTGAAAGTGCTATTTTT AGACACATTTGAGCCTGAGAGCCTAAACACTTAACACTTCACATAATCTACAGATATTT CTTGCTCTGTCACCCAGACTGGGGTGCAGTGGCACAATCTCGTCTCACTGCTGCCTCCAC CTCCTGGCTTCAAGCTATTTTCCTGCCTCAGCCTCCCCAGTAGCTGGGATTACAGGCACA ATCTTGGCTAGGCTGGTCTTGAACTCTTGCCCTTGTTATCTACCCACCTCAGCCTCCCAA AATGCTGGGATTGCAGGCATGAGCCACTGTGCCTGACGTGAACAGGTCAATTTCTATATC ACATCAGACATGAAATGACCTTTAGATACTGACTTTGAAAGAGTTTGAGATGCTATTGGA TGAAACACATGACCCATATGACCAGTCTTTTGAATTGCTGACTCTGAGTATAAAATGTTT TCATTTCACCTTTGTTCACAATGAGAAGTGATCTCTTAACCAAGTAAATGAATTAAATCG ATATTTAAAATAACATTAAATTTCTTGCCAGAAAAACTGTTCTTTCATAAACAAAAAACA AATTGCTCAAAATAAATGACTATATCTTTATTTCTAAAAAATGTTTAGAGATTATTATTA TTGGGTCTTTACAAGTAATTTGCCTTCAATACTAAACACATGAGAACAATGTTTAATATT TATATAGTATTTTACTCTTCAGAAGATATTTGTCCATATTCTCTCAGTTATTCTTCAC AACAACATTATGAGGTAGGTCTTTTTTAATGAAAAAAAACTCAAGTGCTTGAAGTGATTT AAAATCACTGTGGAAGAAAAGCATGGGCATACAGAAAAGCCAAGTGGTTGTGTCAGCT TGGGAAAAGCTTGCAAATTTCCTGTATTTCAAGAGGCCAGGATGAGGTGTAATTATCT TTTACTGGTCTTCAGCTATCCTGTCTTTGATATGTGATTGTGTCAAAACTATGAGGAAAA ACTCACATTAACAAACTTCATAAACTTGTTAAACATAAAATAATAATTTCGATGTTTTAA TTTACAGTAAGAGTTTATTCTTACAAGTCCTTAAATACCCAAAGTTCTTTCAGTTATCAT AGTCTTTTTCAGTAGACAGAAATCCATGTGGACTGTTATTGTTCTGAATAGCTAGGCTAT GCCATAGTAGCAAACAAACCCTGAATTTTCATTGGCTTAGTATCACGAAAGTTTATTTCT TGCTCATTTAACATCTGAGGTGGGTTGGAGAGTCTCCTTCATCCAATGACTCACAGTTCA GGCAGCCTCCACATTTTGTGCACTATCCCTAAAAGGTGGACTCTGTGGTAATCAGTTTCC AATATGGCTTCCAATGACCGCCCCGGGCCCCGGCCCCACTTCCTGATAGTCACATCATC GTGTAGTCCCTTTGCATATTATGCCAGAATTGGTCTGGGTGACCAACAGCTCATAGCAGC AGTGAAACGATGTCACTTTCAAGATTACATAACAGGAGCTTACAGCTTCTGGCTCAAGTA CCCACTTTCTCTAGCTCTTGGATCTCTTCTTCTGGAGGAAGTAAGCTGCCTTGTGGTG AGCAGCTGTTGGCTGGAGTTAAAATCTCCAGCCAGCAGCCAGAGAGAAATACGGTCTGT TAACAACCTCATGTGTGAGCTTGGAAGCAAATCCTTCAGACCAGGTTGAGTCTTGAGGTG ACTACAACAGCCACTACCCCAACCCACCCCCAGCTTCAGTGCAACTTAGTAACAGACACT GAGTCAGAACTATTCAGCTAAGCTTCTTGCAGATTCCTGACCATTCAGAAGCTATGTCAT AATAAATTTTTGTTGTTTGACTTCAGTTTCGGGATAAGTTGTTGCACAGCCTCTAAAGTT GTGAACTAGAAGAAGTATACTGGCTCTTAACCACCTTTGCCAAAAATTAACACTTGTCAG TCATGGTCATATTCATTTGGTCCAAATCAATCATATCGTATCAACCTAACTACAAAGGGG ATTGGGAGATGGTGATGTCTCTGTCACAGAATCTATATAATAGTTAAAAGTATTTTTAAC TTGCATAGACTCAGAACAAGATAATTTGGAGGAATTCAATGCTTAATGGCATACCACTAA GATAAGCTGATAGATATATCGTTGCGATTTGGGTCTCTGACAATAGAGGCAATTGATAAT ATTAAGAGACTATGTGCCAATTATTGTGCTTGGATTGAGGGTACAAAGGTAATAGAATCC AAGGAACCTGCACTCTTTTTGAAAGATAGACACATAAACACATACTTTTAAAATAACGTG GTAAGTGCTACTATGACAGATGGTTGCACAGAATGTAGTGGAAGTATTTGAGAAGGACAC

FIG. 1J

11/51

TTAGCTCTGCTGGGGGATTAGAGAGAGATACAGGAGGAGATGACACCTAAACTGAGTTTT AATAGATGAATTCAAGTTACCCAGGTGAAGAAAATTGGGTAAGGATGTTCTAAGCAGAGG AAACAACATAAGCAAAATCAAAGAGGCGTGAAATAGAATGAGCTATGAAGAAAGTGTTAG GCAATTGGGTAAGTCCAATGTAAGTGCAGATGAGGAGAGTCTGGAAATGAGGCTGAAGCA GTAAATAAGGATTGGCCATAAAAGACCTTGTGTACAATTCTTAAGATCTAGGCTTTGACA CTGTTGTTTAGGGGGGGGCTGTTAAAGGATTTTAAATTAGAGTACCATCATTGGTTTGCAT GAAGGTTTTCACACTGGGGTTTGCATCCTGTTTTGGCAATAAGCTTGTTTTAATGAAAAC AAACAAACAAACTGACAATAAAGAACATAATCCAAATTCTCCAGATAATTACTTCCAGGA GGCTTTCTACGTGCTGCATACAAAACAAAGAAAGAAAACATAAAGTGAGAAAACGAAGG AAAAACAAGGAAAGAAGAAAGAAAGAATACATATTGGAAAAACTGTTGCTGTTTTTGT GATAAAGTCTCACTCTGTTGCCCAGGCTGGAGTGCAGTGGCGCCATTTCAGCTCACTGCA ACCTCCGCCTTCCAGGTCCCAGTGATTCTCCTGCCTCAGCCTCCCCAGTAGCTGGGACTT CAGACATGCACCATCACGAGCAGCTAATTTTTTGAATTCTTAGTAGAGATGGGATTTCAC CGTGTTGCTCAGACTGATCTTTAACTCCTGAGCACAGGCAATCCGCCCACCTTGGCCTCC CAAAGTGCTAGGATTACAGGCGAGAGCCACTGCACCCAGGCGCAGGTTTTCTTTATGATG TTTTAATTATATCTTTCTTGGAACATATATGTATGAATCTTGCATGCCATAGGTCTATTA ATATTTTCCAATATTCTACATGGTTTTTTACTAAAATCATTTTTATGATTAGTTACTGAC TGAGGTTTCAATGCATCACTGTACTCCTAGCTATCTCTCATTTTAGCTTTTACATCACAT TTTGGCCTCACACTGAAACACAAAATATTAAAAATTTGAGATCTAATAAACAATTTTCAC ATTTTCCAACTAAATCCCCACTTCTTTCTAAATTTTCTACAACTTTCTAAACATTCTCAC GACCCCAAGTGAGCCCTTAGGGAATTTCCGTGAATATTTCCCTACAGGTTGGCATGGTAA CACACTTCACAATTTCTAAATCTGTGGATAGTTTAGAAGCTTTTATTTGCTGTTCCTAGT TCACAATGGAAATACAACAATGATTAAAAATTATAATATCCTTTTGTAGATTCTTAGCTT TTATTCCTACTCAGTGACTCTAAAATGAATTTATAAGGCCCATGGTTTATAACCATGTGA GGCCTTGATTTTGTCACTACATTGCTAGAAATGGGGTCAGAAGGCCACCAGCTTTAATAA TTTAATTCATCAATTCGGAATGAATTTGATGAGTCAACCACTTTGGTAGAGAACCATATT GCTCATAAATACTGTTTTGAAGGCAATTCGTCTTTCATAAAATGTGAAGATTGTGCTGAT CTTTCTGGGCAGGGTTATGGAGGTGTGATTAAATGCTTAAGAAACCATTTTGTTATTATA TTAAACCGAATCAACTTTTTATTATTAAAAATAGATAAAAACTTAGCATCCTCAATTATA ATACTTTATACAAAAGTTTCCCAATTTTATATAGACTGAAGATAAAAATACATTAACAAA TCTTACCAGCTGGTTCAGGAAAATAACTTCATAATTATTGAGACATTTATGTGTTTTGGGC TTGATTTATACTTTGGACACAGGAAAACCTAGAGAGATCTGGTTCTTTGAAATCATCAGA GATGGTGATGGTGACTCAGAGATTCCTGAAAATCAGTAAGATTACCCTAGTTTATAGACG TATGTGTTATTTTTCCCCCAGGCATAATGAACTTTATAACTTGTCATTGACAAGAAGCC AAACATGTACATACCTCACACATGTGTACACACACAGTTTGGGGATTGGATGATATGAAT AATATAATTAATACACCCTAATTTTTCATGCAGGATTAAGAAAGTATCTTCCAAACATTA AAAATGCTGAAAACTGGACATAAGGCCTTGAGTTTCCCAAATTCAGGACATATTTTCAAC TATCCCCTGAGTAAATGAACTATAACATTTACAGAAGTAAAAATGATAAATACACTAAAG CTGTAGCATGATTTCTTTTCCTTGAATAGACAATATTCCTTGACAATCTTTCTGTAAACA GAATACAATGTTTCCCTAAGCAATATATGCGTGCTCTAGAGTTTTCACAATTTCTGATCC TCCTATGACTGGCTCCTGCTCACCTCACACTTTCATGGAAGTTCTCTTAGAATGC CAGCTTTGAATCACTGCTCCCTCATGTGCTGTGTGTGATAGCATCCCATTTTAGTTTTGT CATAGAATTGATTACCATTTCAAATTGAATTGTTAATTTATTGTTCATTTTTCTGTTGTC AAGTGTAAGACTTCCAGCAGGAGGAATTTTTTACATATAAGTACATTTTTTAAATTAAGC ATTGCAGGCTTTAAATTTCTTCTATATAAATATTTAAAATAAAGCTTCAATAATTTGAAT TGCTTTTGTGATTATTTTGTTTTATACCTTGAGTAACTTATACATCAACTATTTTGTAGT TATTCTAGTAATGATTATGAAAGACCATTTGAAAATCTTTCCCCAGCACTGAGATCTCCT TGACATGACTAAGTGATTTATACTATGCAATTATATTGCTCTTCTCAAGAAAAGCAAAAT GAAATTTACAAATTTGGTAGCTTTTTGTTCTTTTGTTTTCTCAAGTAAGATACACCAAGA TTTCTTTAAATGATACGCTATATTTCTGCAATAACTGAGAAGAACATGTAATGTGCAAAA

FIG. 1K

12/51

CTCTTAAACTCTTTTTGTTTCAAAATAATTCTTGGTTGTTTTTATAAAAGTCTAAGCAAA TACTTAATGAACTGTGTCCCAAATGAGGTGAAACAGCTGTGACAGAATGTTACTATGACT CTGTACTTTCTATAATAAAAAGGGACAGACATATCCTCACCTGAGCCTTGGGATGTTTCA GGCATGCCCATAGAGCCTAAGCTTTAGGAATCCTCTGTCATTCTTTTCCATTGCCAGTGA CTTGTGCCAATTCTAGGGTTCTGGACTGTGCAAACAATGGAAAAAATAATAACACTTTCA AGAATAGGAGAAACACTAATCCCATCTAATTCTGCCTTCAAACTCCTAAAATATTCATCA CAGGTCTGGTGGCTCATGCCTGTAATCCCAGCACTTTGGGATGCTGAGGCGGGTGGATCA TGAGTTCAAGAGATCGAGACCATCCTGGCCAACATGGTAAAACCCCATCTCTACTAAAAA ACAAACAACAAAAAATTAGCTGGGCTTGGTGGCATGCGCCTGTAGTCCCAGCTACTTGG GAAGCTGAGGCAGGAGATCACTTCAACCCGGGAGACGGAGGTTGCAGTGAGCCAAGATG AGCAGATCCTGGAACAACTGAACCAAATTTATTAATATGTATTATTACTGAAAATCAGTA ATGAACAAAATTTACAGAATGGGCTTCTTGGAGTTGTTACATTTCCCTTATTACATAACT CTTCAATAAAAGTGTTTGTCATACCTATTTTAGTTAATTCTACAACAACTAGTGTGATAG GGCTATTATTTGATCTTTTTTTTTTTTTTTTTTTTTTACAGGTAGTGACATTCAGTATTA GACAGCTGCTATTGTGTTAGTTGTCTGAATACCTTTACATATTATCAACTGGCCTTTTCA $\tt TTCCTGAGTTGTGAGTAAATGCTCTGTCTCCCAGACTGGAGTGCAGTGGCGCAATCTCGC$ CTCAGTGCAAGCTCCGCCTCCCGGGTTCACACCATTCTCCAGCCTCAGCCTCCCGAGTAG GAGACAGGTTTTCACCATGTTAGCCAGGATGGTCTTGATCTCCTGACCTCGTGATCCACC CGCCTCAGCCTCCCAAAGTGCTGGGATTACAGGCATGAGCCACCACCCCGGCCATAAAT GCAGTCTTGTGTTCCCCACTTCCATTCCTCCTTTGACAGTACAGCTATGCTAGTCTGCGT AGCAAATTGAAAAATATGACCTGTGGGATTTAAACAAAACACAGTGTCATACACATTTT CTGGTAAACTTAACCAAAAGGGACTTGGGTTCCATAACTAATCACCAATGCCTCAGTGAT AAGAGCAAAGTCAAGCCAGACATAGATTTTATCTCTTTGTAAACAGGAGTTCAGAAGACC GCTCTGAATGCTGAGTTAGCATCAGCAATAATAGAAATATATGCAGATTGTTGAATTGAA GTCATGCAAAGATATCTTTTTCATCCAAATGGAGGCAAAAGCATCATAGAGCACCAGAGG GCTAAATCCAACTGTAGCAGCAAAAGGTACACAGAAAAATAAAGCATCCTGAACCAACGC ATATTTATTGAACACCCACAATGTGTAATCTGTTCTATTACATTCTGTGGAGGAAATACA GAAGTGAATGAGGCATGGTTCTTACCTACAAGGAATTTCTAATCTTGTGGGGGAGACTAA CATGTAAACAATAAACTATAGTATGAGGATTACTGAAGAGGCATATGCTAAGTCTCAGAA TAGCATTTTGAGTTATTGTTGACATGTGAATACGATTTTGAAAAGTTCCAAAGAATGAAA AATTCCACCTACATTGGTGAAGTACTAAGATTAAATGCATGATAGCTTGAAGACACAAAA ATAATTATTATAAACCATTCCAAAAATCATTCAGGGAATTCCAATAATACACAAGTTTT ${\tt TAAACACATTTCTGGGTAATTTTGAGTAATAAGGTCTTAATCTCCTCTACTGCTTTCAAT}$ TGTTTTTGTGGCCCTTCTTTATTTTGTGGGTATCTGGCCCAGTCTTGTCTGTAGTGTATTA TGGTGGATTGGATTAAACATGTTTTGCAATCTCTGGAGTGATTTTAAAATGACTTGTGTT ATATCAGAGTTTCCTAAAGGGAGATTAATTTGGCTTAATGGTAAGAACGGATTAAAGTTA TGAGATACCAGACACTGGGAAAACAGTTAGAAGCCTGTTGAGACTCTTCAGGGCAGTTGT GGCAGTCTGAAGATGGAAGTTGGCAACTCATCAAATGTGAGAAATTTATAGGAACAGAAA AGAACCTGCTGATTAATATAAATTTTCTGCCAAAGAAGTACAGTGGCTCTCCTCAGCAA ACTAACATGGGAACATAAAACTAAACACTGCATGTTCTCACTTATAAGCAGAGCTGAACA ATGGGAACACATGGACACAGGGAGTGGGACATCACACACTGGGGCCTGTTGTCGGGACTA TGGGAGGGAGACCATCAGGATAAATAGCTAAAGCATGTGGGACTTAATACCTAGGTGATG GGTTGATAGGTGTAGCAAACTATGATGACACACGTTTACCTATGTAACAAACCTGCACGT GTATAGAAGGGTCATGATGAATTGGACAAAGATACGTGGAGTTTGAATTGCTAGAGGAGT ACCCACGTGCAGTTGTCCAGCAGAAATCAGGGCTTGTTCCCCAACATGCTATTCACAATC

FIG. 1L

13/51

ATGTGAAAATGTTTTAGAAAATGTCTTCTGGAATAATTAAAAGCATACAAGGGAATGTAA ATCTCTTAATGTGACAAGACCTTTTTGCCACAATAAACAAATTCATTAGTTCAAAAAAATA TTTATTGTGTGCCTATTGCAGCAAACAAAACAGACGAAGCTCCTTCTTGTAGGGAACTTA TACTCTAGTGATATTTAGTATATTTTTGACAATTGAACCAACAGGATTTGCTGACGGAT AGGTGCCATTTACTGAGATACAGGGCCGTAGAGGAGGAGTGTGTTTGCAGCAGGGAAGGA GAAGACTCAAAATTTGGTTTTGATCATACTAAATTTGATATAGTACAGGTAAGTGTATGG TGGCCATTAGAACATGAAGGTAAGAGTTTAGATAAGGAGACAGGTATGGTGAAATACATC CAATATTTATAACCAATATTATCTTTTGTGTCTGTACCTTTTTATACATTCCCCATATAT ATCAAAGACTATAGAAGGGACTGGATAGTGAATAAGTGATTATACATAAATTCTTTTTTA CAGATTATTTTGCTCTTGATTTCTCCTATGTAAATCATCACAGCTACATTTTTTAAAATC TTAAAAAGGATTACTTTGAACAATGCATTTAAACATCCAGAAAACAAAAACAGGAGTGCA TGGTAAAAATTCTGATTTCAGAACGTATGCCTGACTTATCAAGTCAGAATTTCAGGGAGT GAAGACCCTGGAATCTACACTTTAAATAGAGCCTCAGTTCACCAAGTATGAGAAGTCCTG TAACAGGGAAAAGTAACCTCCTGTTATATTTGATGGAGGCCAATTGACAAGCCAAGTAGT TTTCCATTTGACAAAAATTCTATTGTACCAATGAAGAGCTATCAGAGGGGAGTAGATTAA AACACCTCCCTTGAAATGGAATTTGGCAAGAAAGCAAGAAATTACAGCAAAAAAGACCAAT AAGAGGAATTAGGGGCAATGAAGGAAGGAGCAAAGATGTGGGAACCCAAAAAGTTTTCCT TACATTGGTGTAATTTATTATTATTAAGCCAACAATATACTTTTAAACTTATACAACT TTGCAAAAAGTACAAATCAGAAGTCTGGGCTAAGTAGAATGCATAATAGAATCAGTAGT ATTAAAATGAATGTCACTTCTTTTTACCATGTGTCCTTTAAATTATTAAAATCTATACAC ATATTGCTATACATAGTAAATATAGTTAGTCAATTATGTCATGGAAAGAATTGAAGGGTT GTTATAAATTTAAAGGTGTTTCACTATACAAAAACATTGTGAAATACTGGTGCTGATTTA GTTCTAGTATCTCTGATATATTAAATCATAAATGTCAGGAGTTATTGGTCACAAAATAAA CACCAGAATTATGACAGTCTAAAAACAAAAACAAAAACTTCAGCAACAATATTGAAG ATATGGAAGTGCCAGAAGAATAAGGATTAAGACAATGAATAAAAATCTCTTCCAAGGACT GGTCTACACTAAGAGTTTAGAAATGCATTTTTTTTTCACAGAAATATCCTTAATCCTCTA TATAGAAATGAGAAGAAAACATAAGACTTTAGCAAGCTCCATCTAATCCATTTGCAGACA TATGGTTACCTATCTTTCTTCAATATATTGGAGTTTGCAAATATTCTACCTTCAAAGAA TAGGTGTTACCAAAACATTGTCTGCAAGATTTCTAAGATTTGAAATATATTTGCTATAGT AGGTTAGAGATGAGACATTTTTACTTTAAATTGCAATAATTCAGACTTAAAATATAAAAT TGTGTATACTCATATGAACTTTAAGGAAATATCAGAGGCATCAGTAATAGATAACTTGCA TCTCTTTTACATTCAGTTCAAGCTACTCAAATTTTAATCTTTTGTTTTCATTCCAACAAA AAAAATTAGGATCTGCCTTGGCTTTTGCTAAGAAAGTAATTATTGGCTGGACATGGTGGC TCACATCTGTAATCCCAGTACTTTGGGAAGCTGAGGTGGACAGATTGCTTGAGCTCAGGA CGCGCGCACACACACACACACACACACACACAAATTAGCTGGGAATGATTACACGC CTGTGGTCCCAGATACTTGGGAGGCTGAGGTGGGAAAATCACCTGAGCCCAGGAAGTCGA TTATCTTCAACACTGTGCATACACACTTTTCTGCATCTAGATCCCAAATTTTTGTTTTGT ATTTACATAGAACATTGATAAGTAAGGTAAGTATTAATTGATAAAACATTTCAAACTCAT TTTTCACTAAATCCAATGGCCTTCCTCTTTTGCATGAAGTCTCTAAGAATCATGTTAATC TACATACTCAATCTACGTAACAACTGGATATATCCTGTAGTTGTTGCCCATTTTTCTGCT AAATGTTATCTTTAGCACTAAGCATGAGTATGAGGAAACAGTATCTGTGCTCAGATTCCA GAAATGAAGAAAATGTACTGGAGGTCTTTTGGATAATGGCTACAAGGTCACAGGGACTGA CTCCTTTGGAAGCTCAGCGATAACCATTTTCAGAGAGAATATGTCAACATCTTTCAGTCT AGAACTTGATGTTCTGCTGAGATCTAATCTGGGGGTGTCCTACTATTGAATAGGTATAAA ATATTGAAAGTCTATTAATTGGCAAGCACTCTTCTGACATTAGAAGGAGCAAAGATAAAA AAGATATTATCATTAACCTCAAGGACATGACAGCATCATGGGAAGGCCAGAAATGCAATA TGTTAAAGTAAAACACAGTGTAGTGTTTACTACTAAAGAGATATAAACAGAGTACTGTGG TCTAAAATCATATATAACATTTGCTTAATGGATGAGAAGGAAACTTTAACTTCAGGAG GCAGAGCATTAAGAAAGTGAATGACAGGAGGGTCAAAAGAAAAAGCCGACAGTGTTGCAG AGGCAGGGCATAAAGGAGCTAAACCTTTGCTACCTTCAGTTTTTATTATCCACAGAACGA

FIG. 1M

14/51

AATTTATGGGGGCATTCCTATGGTCCTCACCTCACCCCATTTTTCTGTTTTACCTATGAA ACTTGATCAAAATACTGTCTCCACATTTCTCATAAAATACATTAGTTTAATTTTCTACTA TTACTTTCTTTTAGTTGATTTAAAAAAAGGTCATTTATGACCTATTTAGGTTAGCATCAT TAATTTTATCAATGTAAGAATATGGTAGTACAGTGTGAATTCCATTAATGGATATGTTGA TACCATGGGTTTCTCTGACCTTTCCTCTTCCGCTCCTCCTGATGATTGGTTCTGAGCTT TTTAACACTGAATAAAGATTTTTTTTTTCTCTAACAGACTTAAAAATAGTGCCCTAAAAAT AAAAGAAAAACAAAAACAAAAATAAACATTGTGTCCTACATTTGTATTAACTTTCTTA TTGAGTTTTATTGATAATACCTTTAGGATGCATGTATTATTAGAAACATCAGTTATTTAC AAGTTCACCTATTTAAAAGTCTAATAGGAAAAAATATTTCATGTTGCTAAGTATGTGACT TCCCTTTAAAAGATAATAATGCTTTCCCTTTAAACAACAATAGTAAAAGAAGTAGAGTTC CTTTTAAACACATACTTTTATATTATAACCCATTCTGTTTAAAAAATAGCAGGCATATAA TCTAGAAATGCAAATAATTTAGTGAAATTTTTTAAAATTATTCTACATATAATTAAATATG GATATTCGTTTTCAAATATCAAATAATAAAATATGTCTGAGATGCTGACTAATCCTTAAT TATAGGTGTGATTTCTACTTCACCATCAATACTATGGTACTCCAAATCTTAACATGAGTC TGATTTTCTAATAAACATGATGAAAAAAGTTATGGAAAAATTTTGAGATTTACTTTGGGA GGTTCTATTGTGTTCTGTTCAGCTTCATAATATTCAGTTTCTATGAGTTTTGGTATTTAAT TATGTGTGTTTTGTCATTCAGTAGGCTGGAAGTATGACCATTGGGAGATCAAAACGATAAG ACATTAATGACAGTGCTTTATCACTGAATCTAGTACTTTTTTTAATGAAAGAGATGTTGG CCTCTTGTATTGTTATAAAACAACACAATTTTATGGCTTTAAATTAAAGTACAATCATAA CAGAAGACAAAATTAGATTAAAAAAACAAACATGGAGTGACTCATATAAAATATTTAGAAA CCAATAATACAGATAGAGACACATTAGTTCCTCTAGACATTGTGTTTTCCAGTAAAATGA TCACCAAACTTACCAGGAAAATGATAATTATCAGATTATTTACTTTCAGAATTAAAGGCA GGAAGAGAAAAAATGAATGAAGAGGAAACACAGTAACCATATAGGACAATAAGAGTGAA TGAAGATAAAATGAAAAATCAATAAGATATCGACTTTCTTAAAAGACAAATATCACAATA GGAAACACCTCAGAAAGGGAAATCTCAAGAAAATAATAAACTGAAAGAAGAAAACATATC AAAACAACTTGAGGACTGACAAAGTTTTAAAATGTATTTAGATAAAGATACCATGAGGAA AGTGATCAAGGTGTTCTAGGTAATCACTGAAGATAAAACTAAAAATAGCTTAAATTAAAA TGAACATCTTAACAATGTCTCAAATGTCAGGAATTGATCCAGTTTTTTGGCTGCACAACAG AGTGGCTATAGTTAACAATAATTCACTGTATATTTCAAAATAACTCAAAGAGTAGAATCG GAATGTTGCTAACACAAAGAAATGATAAATTCTTGAGGAAATGGATATCCCAATTACCCT GATTTGATCTTTACACATTGTATGCTTATATAAAAACAGTATTCATGGCCGGGCGTGGTG GCTCACACCTGTAATCCCTGCACTTTGGGAGGTCGAGGTGGGCGGATCACAAGATCAGGA GATTGAGACCATCCTGTGAATGGTGAAACCCCGTCTCTACTAAAAATACAAAAATTAGC CGGGTGTGGTGGTGGCCCCTGTAGTCCCAGCTACTGGGGAGGCTGAGGTGGGAGAATGG CATGAACCCAGGAGGCAGAGCTTGCTTGCAGTGAGCTGTGATTGCACCACTGCACTCCAG CCTGGGCGACAGAGCGAGACTTCGTCTCAATAAAACAACAACAACAACAACAACAACAAAAAAC ATTTAAATTTTTCCTATAGCATAGAGATCTGTAATTAATACTTGTCGATCATTGTTGTTT CTGTCTTCCCAACACTACACTCCTGTTTCTTCACATTCCCCCTTCTTCTAACAGCACTA ATCAATCACAGTACCCCAGCAGATGGGACCAGAGGCAAAAATGCCTGACCTTCTCCCATC CCCCAACCACAGCAGCAAATGAATTATAATTTGATGCACAAGGAAGTATCGGAGCTTTTG TGTTGGGTTTTACATATCACCTGTGGGAGATAAATGAACTTTTCCCCACCTAACCTTTAG CCACTTGGGATGATTAGACATAGAGGTGCCTAAGATCTTTCCCTTTGCCACATTAAAAAC AAATCATCTATGGCACGAGCATACAAGACCAGCTTTCAGAGACACAAAATGATGGAGAGA ACCATGATACTAGTTTTAGACCTAGTCACTGAGACTTTCTCTGCTCCTTCCCAGTTACCT GAGCTTTATTTTGTTTACATTTATCAGATTTGAATGGCTGTACTTCAAAGTACTGATTAA AATAGGAACCAACCTATATGATTCAGGTGGTGAGAAGGAAAAAAGAGAGAAAATGAGG TTAACAAAAGAAATAAAGAAAAAGAAAGAAAGAAACAAGAAACTCTGACTACCTCTCC TCTTTGACATAGTTTACACTTCTGACAGATTGTTCTCTCTAAATTTATGTAGAGATTAG AGTGAGGATGATGTATGCACTGTAGCATGGTTGTTCCAGGAAGCCTTGACTGAATGA

FIG. 1N

15/51

GGCAAGGAGTATGTTGCTCCCTCAGTAACCTCAAATTTACCTGCAAGCCTGATAAAAATC TAACACTAACACTAAACCCAATCTTATCTACAGCCCTAACTGCACCCTAATATTAACAAC CCTACCTCTGTACTTCAAAACTAAACTAATTCTGATTTTACTCCCATCTGCCCCTTTTA CCCTAAAACCAACTGTAAAACTAAATTTAACTCTAAACGTAATCCTAAAACTAAGAATTA ACTAACAATTTTATCTCTATACCCAACTGTTAACCCCAAGCCTAACTCTAATCCTATCTC TAACCTAACATTAACCACAAACCTACTTCTAACTCTAATCCTAACCATAACCTCAAATCT AACTCTGATTCCAATTGTAATCTAAACACCAACCCACCCCTACCCTTTTATCCCAAATCC ATCTGAAACCCTCATCAGAACACAAATTCCAATTCTACTTCCCACCCTGACTCTGACTCT AAACATAGGCCCAAATATAACTCTAACTCGAAGTCAAAAACTTAACAAACCTTATCTTGA AACTCAACCTTTACACTAACCCCAATTCTATCTGTAATCCTAACCCTAATATTATCATCA AACCTATGTCTAACACGACCTCCAACCCAAAACCAAAACTAACCTCAGACCTAACTCTAC ATCTAATTATAACCCAAACCCCAGGCTGCTACTTACCATAACCCTGAAACTAAGCTTGAT CCTTTCTCTTTTTTTGAGATGGAGTCTCGCTCTGTCTCCCAGGTTGAAGTGCAGTGGCG TGATCTCGGCTCACTGCAAGCTCTGCCTCTCAGGTTCATGCCATTCTCCTGCCTCAGCCT CCCGAGTAGCTGGGACTACAGGTGCCCGCCACCATGCCTGGCTAATTTGTTGTATTTTTG GCAGAGATGGGGTTTCACCCTGTTAGCAAGGATGGTCTCAATCCCCTGACCTTGTGATCT GCCTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGGCATGAGCCACCACGCCCAGCCGAC CCTTTCTCTTAACCTACACTAACACTAACTGTAAACCTAGCTGTAACTCTAATTGTAAAC CTAACCTGATTACTCACTACAAAGGTCCCTCTAATTCTAACAAGAAACTCAATCCTATCT CAATTCCACCCAACCCCAAAAGTAAATCTAAACTTAAACATAACTCAAAATGTATCTCAA ACCTTAACCTTCACGAAACTACATGTAGCACTAATGTAACCCTAAGCCCAATCCTATCAG TAACACTAATGCTAAAACAAACCCCAATCTGTATCTCTACCCCATCACTGACACTACCCA ATATCTCCAACCCTAACCCTAACATTAACCCCAAACTTATCATTAATCATACATCTAGCT CTAAACCTAACCCCAACTTTAACTCTTACCCTAGCTCTAAAATTAACCCCAACACTATCT CAAACTGTAATCCTAATGCTAACGTTCAGGCTACTTTTAACCCTCACCCTACACAAAATC CTGCACCTAAACTCAACCCTAACTTTAAACCTACCTCTAATCCAAACACTAAATTTAAAT CTGGATCACGACTTGGGCATACTAGCACCCACTAGTGTTCTGGGTGTCATTTCTTTGCTT CACTCTCATCCAGCTTTCTTTACTAATTTTGGATAATGAATCAGAAAATAGTGGTGTGGA ATCAGGGTCTTTGAATTATTGTATTATCCAGAGTTTGTCCTGCTGCAAATGATAAAACAC TTATTGGCTCAAGGAACAGAAGAATTCAGTACTGAGTTTCACAAATACCTGGATTCCCTA TTGGATTCATTGTTAGGTTTCCTGTGGCAAGATGAAATGGCCTCAGGCCTGTAACACAAT AGGATCAATTACAACAGAAGATAGTATTTCTGTTTTCCTGGTTGCTCAAGCCTAAATTCC AAGATTAGTTTATATCAAACCTAGTTAGTTTTGCTCATGTAAGGGATTACTGCAACTGGG TACACTAATATGAAGAGTGGGAGAGTTGGTTAAGGGGGGTTCTCTGAAAGGAGAATTAGGT CAAATGTTGAGGAAGAATTTTCCTTTATGATCATCTAGCCCAACTTTTTAATTTCTAATT TTGTGGTTTTGACCAGTTTTTTTTTTTTTTTTTAATGCAGCATGTCATAAAGTTGGGAA TACTTCACATTTTGTCTTTGAAAATTTGGAGAGTACTTAAAAAGATTTACAAAGGGGAGG ATTGAATTATTTTAGGAATGTAAATGGTGGTCTTCTGTCTCAGGCAATGTAGATGCTTGC TAGAAAACAGCTGACTCATGACTGTTTTCTTTCTAATTCATTAATATGAATTATTTCAAA CTGCAAAGTTATCTCCTTTCTCCTAATCTATCCACTTAGAGTATACATGTTCAAATT AATGTATTGAACTAATTTTTCTAGTAATACATTCTATGCATTACAAAAATAGCAGTGGGA AGGTGAAAACAAAATGCAGTTATGCATTTATCTCTAAATGTGTTCAACATCTCTTATGCG TACTTCAAAATAATTACATTTGTTTAATTTTGAAAAAAATATTAACAAGAAGTTGTAATT TGGGGAAAATTTAAAGCTGGCGAAAAAGGCTTCATCATAATTGACAATATGGGAAAATAC TGTATTAAAATCCTAGGTTTCTCCCTTGTTTGCATGAAGGAAATGAAAAATATATAAGGG AAGGATTTAATCAGTCAGGCAAAAATCTAAATTCATCACAGGTTTATTCACTGCATACTA TAAATGAGCAGAGTGTGGTGATTAAAGGTTGGTATTTGGTGCTGGGTAGACCCAGCTTTG CCACTTACTGCCCAAGTAAATATTGCCATCCATCAGATATCTCCACCTATCAGACCCACC CTGTTGTAATAACAAGATTAAAATCTGTATCACTAAAACTTTAAAAGAATTTATAGCCGA TGTGTGTGTTTTTGAAACGGAGTCTTGCTCTGTCGCCTAGGCTGGAGTGCAATGGTGGGA

FIG. 10

16/51

TCTTGGCTCACTGCAACTCCCGCCTCCTGGGTTCACGTGATTCTCCTGCCTCAGCCTCCT GAGCAACTGGGAGTACAGGCGCACCACCACCCACCCAGCTAATTTTTTGTATTTTTAGTA GAGATGGGGTTTCACTATGTTGGCCAGACTGGTGTTTTTTGAAAAGACTTTTTCCTGATT CAGAAGGTGGGACTCACAATTGTAATTCTGCTAATGGTTGTCTTTCAGTCTATCAATTGC TTCATAAATGCATCCACTGTTCCTTCTTCTTCTGCCCTGCTTATAATTTTCCATGAGTCC ATATATCTTTTTACACTGTCTTTAGTCTTATTCACTAAATTAAAAACTAATTTTTGATAT TTGGTATTCATGACAAGACAATTAGTAGAATTTTGATGCTTCTTGTCTGCAATTACAGAA TCAATATATTTCTATATTATTGTATATTCTCTAAATCTTATTTTGTATAATAGCTTTCA GCATGTTCTTTAATTCTGTTTAGATATTTAGAAAGTATTTGTTGTTATTCTGTAATTTAT TTCAATATTCAATTATAGTTTAATATTTTGTTATCTAGTGTTGTCTTGATTTTGATATAC GTACTGATTTTGTAGATCCAAATTCCTCTTTCCTATCAGAGAATGCAATTTTTTACTTGG ATAAATAAGAATCATATCTCCTCTGCTTGCTACCGTATTGCATACATTCATGGGTAGAGA ${\tt AAGAGTTAAGCTGATGAGAGTAGGAATTAAGGTAGACCTGTTTGGTAGGTTCTCCCAGAT}$ TTCAGAGGACAGCTTTTTTTTCCCTGCCTTGGTCATTTAAACTTTTTGGATTTTGGA TTCTCTGCTTTAGGCAGAAGCATATGTAGTCCAAGAATGTGCTTTTCTATCCAGCTAC ATCAATAATAACAATTAGTAAAATTCTACTTAAACTTAGACCTTTGCTGTTCTCTTTTCT CTGCTTGTGTTAAGTCATGCTCATGATTCTGGCAGTTTTCCACAGTACCATGTACAGAAA GCTTGAATAAGGTACATCTAGAATACTCATATATGTTCACTTCAAAAACACATTTTTGTG GAATTCTAAATGCAAATCTCAATAGTGCAATTCTAATTTACAATGAGAAAAAACTAAGGG ATTTTTTCTGGTGATTCTTTTTGCTCATTTATAAATATGTTTTTAAATGGTAAGCAAATA TATAAATTAAGCTTTTCCTTACGTAGCTACATTGATTTACTAGTGGTGGAAAAGGTTAAG CAAAACTAATTTTCATGAGTGTAAATGAATTAGTAAGTGACATATGCAATGCTTAAGGGG AATTTGCATAAATCTATGACTGATACTCAACCTCTTGCTTAGCGAGAAGATAATTAAAAT ATTTTATACTTCAAGAAGACCTAGTTTTCCAAATTATTTACATCCACAAACTCAGATTTT ATAGCAAGTAAGAAAGTTAAGTCAGAAGCATATACTATTAACAGCTACTTACATTGCTC AAATTTAATATACGATTGCTGCTTTTGTTGGTTTTGAAATGTTTCTTGACCATGGATCTG GATACAATAATATTAAAAAATTAAATGTAAGTTCCTGCACTCACAGTAGAGGTAAGTTCA CAGATTAAATAATGTGTTAATTGTGCTTCTAAAACAGCTTTGGTGATCTTAATAAAATAA ATATTGTTTTTATTTCCATTTTTGCTTTTCAGACAAGAAATGCTACTTGATGGCTGCATA TATTTGTTTTGTCTCTTTTCACCACCTACTCTTGCTAAATACTCTCAACCCACTCATGAA ATTAAAGCACATTGGAAAACATTTATCAACTACCTGTAAATACAACCTATGCTCTCTTT GTGGAGGTGATAGACATTCATCAATGGAATAGTTGATCTAAATCCTAGTCTTCATTATCT TGTTTTATACATTCTTGTCTTAATCAGTTTGGGCTGCTCTAACACAATACCATAGACTAG GTGGCTGATGAACAACAGAATTTGTTTCCGACTGTTTTGGAGACTGGGAAGTCCAAGAT CGAATTTTATGTCTGGTGAGGGCCTGTTTCCTAATTAATAACATCTGTTGTCTCATATG TCCTCACATGATAGAAGGGGCCAAAGGAGCTCTCTGATGTCTCTTTTTTAGAATATTAATC TCGTTCATGAAGGCTCTGCTCATGACCTATTCCTTCCCAAAGGGCCCACTTCCAAAGA CCATCATATTAGGGATTAGGTTTCAACAAATGAAGCCAGGGGGAGGTTGGTAAACATTCA ATCTATAGCAATGCCTATCTCCAGGAGCTGCCTGTGGAAACACTTTTATCTGATATGGTA GTTTAAAGCATGGCAGGGATAAGTGGTATGAGGAAAACTCTCCCTGCCACCCAACGCACA CATCCCACTTAAGCTTCAGCAGCTCCAATTTTATCTGTGTAATATTTGGTTCCACATCAA AGTTGTTTTGAATATACTTCCATTACCTTAAAAAATGTAAAAACACTGCTTTAAAAAAGCC AAGCCTATTCCCTTTTCATTATTCAGAGTTCTTCCAGTTTTACCGTTACATCAAATTAGA ACTACATAATTAGGAACCCCTCTCTAAATTTGCCTCTATACAGAGAAAAACTGTGCCTGA GGACAGAATTTGTACTTCGTTCCATACATAAAAACTCATTTGACAAATAACAAGCATAGC TCCAAGCTCAAAGAATAGCTTAATTTTTCCTGATTAGTTTATATCTCTCTTATTAATCAA TGACATTTAATATTACAACCATAGCTTGGGGTTTTAGTTTATTTGCTTTCTATCTTTTT ATACTGTCGGCCTACCTGTGCCCAACTATGTTATAGTCAGGGGTTGGTAAAATAAAGACA AAACAAATCCTGTCTTCCTGGAGATCACCTTCACTGGGGGTTGAGAAACAATAAGAACAA GTAGTAAGTAAAATATGTACATTAAAATTTTAGATGAAGTTAAGTGCTATGGAAAAAAGT AAAATGGAAGAGGTGTTATGGAGTACCTGTTCGGGTATGGGTTCAATTTACAAGTGGATG GTCACCTTCTCACTGATAAGGTGACATTTGAGCAAAAGTCTTCAGCAGGAAGGGAAATG CCATGCAGTTATCCTAGGAAAGAACATTTCCAATATAAGTAACAGCCAGTGCAAAAGCCC

FIG. 1P

17/51

TGATGTAGATGCATACCTTAGGTATACGAGTAACAGTAAGAAATTAGTGGCACGAAAGAC AGATGTACTTGGAAACCAAAAAGAATCTCTGGTAAGAAATTGTAAGTCATTGTAAGGACT TAAGGTTTTTTTTTTCCTCCCAAATGAGATGGAGATCCATTAGAAGGGTTTGCGTAGA GAAATAATATGATCTGACTTATATTTAACAGGACTACTCTTTTGCTGAATTGAAAATTGT CTCTAAGGGTGTATATCAGATCTTATATTGATCTTACCCTTCTCTGTTCAATATTTAACA ATCCCCTCTCATAAGGGCTGTGAGGGCCTAATCTGCTTACCTATCCAGCAGGCTGGGAAT GACACAGAGCACTCACCAGGAGCACTCTCAACCTATGACTCATGGAAGTTGGTAGATGAA TACCCCAGCTCTCATATTCCTTGGGTGGAAGAGCTCTGAGATGTGTGTTCTACACCATTA CCCAGAGGGCACCCTCTGGATTAGGCTCAAGTTGCTGACAGTAGTATCTTGCTGACTAAC ATAATTTTTATTAATTTTCTCCCCATTTGACCTTATTTCTCCATTTTTCTAATAGTGTTC ATTGGTATCACTTCCAAAATAAATTACCTTTACTTGAATATTTTTCTTAGAATCTTCTAT ACAAACCTGAGCTAATACTGGGGCAAAGAGTGGAAGCAGGGAAATATTTTGTAGGTGTTG TGGTGATGTAGGACAGAGCCTGATAGCTTGGATCAAGGTGGTAGCAAAGGAGATTGTAGA AGCTATCACACTCTTTATATATTTTGAAGACACAGCCAAGAGGTTTGGTGGAAAAATGGA TTGTGAGAAGTAATAAAAAGAGTGGGAGAGAAAGTCAAGGATGTCACCAAAGTTGTCCTA AGCAAGTGGAAACTTAGATTTGGGAGAATCAAAAATCCTAAAATATCCAAATCCTCTCCC CTGCCTTCCCCTCCCCTCCCCTTCCCTTTGGAGATAGGGTCTTGCTCTGTTTCAC AGGCTGTAGTCTAGTTTCGCGATCTCGACTCACTGCAGCTTCGACCCCCTGGGCTGAAGT AATTCTTCTACTTTAGCCTCCCAGGCAGCTGGGACTACAGGATTGCACTAATGTGCCCAG CTCAAGCAATCCACCCTCCTCAGACTCCCAAAGTTCTGGGATTACAGGTGTGAAACACTG TGCCTGGCCCAACATTTTATTTTCAAATATTTAAGTTTTGAATGTCTATTCGATAACCAA GTAAAGAAGTCAACTAGAATATATGAGAATGGAGTTTTCTAGAGAAGTCTGGGTTGAGGA TGTACTTTTGGGAAATGGAGCACATACTTGGTATCTAAAGCTGTGAGCCGAGATGAGATC ACTAGGTAGGTAAATATAGATAAATTAGAGAAAATATCTAATAATTGAGACATGGAGTAC TATCATAAATTTTGAAAAGACAAGAAAATGTGAGAGATCGAGAAGAATGGCTGGGGAAGA AAATGCTACTGATAAGTAAAGTGAAATGTAGAATGAAAGTCAACCATAAAATTTGGCATT ATGGGGATCATTAATGACCTTAAAGAAAGTGCTTTTAGTGTAGTAATAGAAAGATGCAGA AAGTAAGTAGAGTGAATTCAAATTCAACAGAGAATAGACAGAGAGGAATTGAAGACATTT GGCAAGTGTTTGGAGGCCAATTTATACTCAAGAATAATTTCTTGAGTTGGTTTTTTGTGT TTGTTTGTTTTTGATTGGTTAGTGTTTTTTTTTTTTAGACGGGATTGGAGAAATACTTTC ATTTGTGTTTTTACCCATGTTTTCAGCCTTGCCCTGGCTGCCTGGTATAACGCAACTCTA TTTGTTATTCTGCTATTATAGTTTCCCTAGCTTGAATTTTTTTACACCCTTATTATAATT GTAGCGTTGCATGCCTATTTCAAAACATCTCATGTACCCCATAAATATATACATCTACTA TGTACCCACAAAATTAGAAATAAAAAATTTAAAAATTATGATTTTTTAAAATTTGTTA TAGTTGAAGGAAATTTCAGATATTTTGGTAGCAGAAGGAACTGAGTTATGGCTCAAGAGT TTTTTAATAAGTGTGAGTGGAGTTATACAAACTACTCATTAAAATCTTTATTTGAATTTG TAATATCTGAAACCATTTTCATATTGAAGAATCACTTAAAATAGTCATAAAATGTAAAAT TGCAAGACAATTAAAAACAAAAATATGATTTCACGACTGTGATAGTACCTGAGAAATTTC TTCATCTCCTTAGTAAGAGAAGTATTACACCTATTTATAGTTATTTTATGAAACTAGCTA AGATGAATTATGTAGAAAAGATACAGATTTTCAAACAGAAACTAGAATTAATGGAAGCTA AGCGAAAAATAGCATCTACCTATAAGGATTTGCAAAGCCAGTAATCTTTCTAAAAATATC AGCAAACCCAGAATTAAGGCTTATGTTCTTAGCTCATTGTAACTAGATCAAAAATAAAGA AGGCCAAATAAAGGTATGTGACATTTGTTGAAAACCTGAAGTGTCCTATATGCAGAAATA TTTTTATCATTTAATTTAATTTCAGAAACTTCTTAACATGACATGATCCTCTTGAAAAGAT CACATCAAAAAAGGCAAAATAATTGCATAATTATTGTAGAATAATTTTTGTGTGAGTATT TTTAAAATATGCCTAATTTTCCAGGCATTGGTTTGCTTTGCTATAAAATGGGAGGATAGA AAATAACTTTCAAAATATCTTATAAATCTAAGAATCTTTGCATCTTATAAATCTAAGAAT CTTTGGAAATTCATAGATTATTGAGATGGAGTCTCGTTGCTATGCATTGTAGCAAAGTTG

FIG. 1Q

18/51

GAAATAAATTCTAAATTTTATTTCATTTATATTGATCAATAAATTGTTACATTTCACTAA TACAATAAGGAAAATTTATTTTACCTGAGTGTATGTCTAGCTTGTGAAATAAAAATGCTC AATTATGAAAGCATTTATTGCCATTTTGAATGAAAAATGTAATATGTAGAACAGAATTTT TTTTGCCTTGAACTCAGTTAAATGTAGAAATTGATAAGGACTTGCATTTTCATGAACTTA ATAATTATCTGTCTTTTCAATGGTCTCCATATCAAGTCTGAGAAATATGGATGTGATTTA TTTTAAACCTCACCATTTGAAGTAAATCTAAAGATTCCATTAGGTTATGAGCATATAGGA TACAAGGACCATATTGACAGTTTTGTGGGATTGTATTAGGATAAAAGGGTAGGAACAATG GGGAGAAAATTATAGCTTACAATAGGGAAGAACCAAAAATTGTTGCAAAATGATGGAACA GGCTGAAAGAATGATATAACCTCCTAAACACTTCAAATGTTTAAGCAGTTCATTGTACCA TTAAAAGTCTGCTACAACTACAGATAGAGGAACAGTTTGTAGTATCCGTGATCCTAGAAC AAATTTAGCTTTTAATATCTTGTCAACTTTTTTGTTTTAGTATCTCTTCCTTGGAACTAG CTGAGCTTTAATGGCATCATCATGTGATATGACTTGAGATTTATATTTTGGAAGAGCTTTG AAAAATCACGGATTGTTACCCTAATGAGGTGTTATTCAGTCTTTTAAACAAGAGCAATTT ACTTGGCTGGGCATGGTGGCTCACACCTGTAATCCCAGCACTTCGGGAGGCAGAGGCTGG TGGATCACTTGAGGTCAGGAGTTTCAGACCAGCCTGGCCCAACACGGTGAAAAACAGTCT CTACGAAAATAAAAAAAAAAAAAAAAAAAAAAAATAGCCAGGTGTGGTGTGTGCCT GTAATGCCAGCTACTCGGGAGGCTGAGGTGAGAGAATCACTTGAACCTGGGAGGTGGAGG TTGCAGTGAGCCAAGATTACACCATTGCACTCCAGTCTGGGTGACAGAGCGAGACTCCAC CTCAAAAAATAAAAATAAAAAAAAAAAAAAAGAATGAATTGCTCATAAATGTGCCTCACTGAT GATTAAATTTAATCCTGCAAGATTATGTCTTTTGATGGAAATGAGAGGGTTTATACAAAG TTTTATTCGTGATGTTATCTATGTCATCTATTGATTTCTGCTCTGATTCATGTGGATGAA GTTACACCTCACACTTTAAGCTGGTGTCAGTCTTCCCATTTTCTGCTGTGATGTGTACTC AAGATCTCCAGATTACATCTGTAATGTAATGCAGCCATGATTGTTTATAGGTACATTTAG ATGAATTCAATGATGAGTTATGTTGTAATAAGTGTCAGATTTAGATGAACCATACAAATA AAAGAACCATGCATTAAAATGACAAATGTGTAAAAGCATTATTTGGGCCTTAAGTCAAGG CCCAAATGTGGATACTGGTACTGAGACATCTTTCAGAAAGGAGGTATGAAGTACTGAAAA ATATTTACAAAATGAAGACTACTTTTATCTTACTTATCATGATTCTTTTATTACATATGC ATTTTCTAAGATAACTATAGTGCATTAGTTTGTACTATGTTAATAATAATAATAGGGTAAA TCAAACAATGTTTTCTAAATCCATTAAAATAGAGTTCCCTAAGGGAGTTAAAACAATTAC GTTCTACTGTATATTATTGGCATGCTTCAGGAGACATGATTTAATCTCTAGACTATCAGA ATTCAAGAACTAGTGAGTCATATAACAAAGGAGGCTTAATCATGCCATTTAAGTGTCATG GAAAAAGGTTTATTGGTCAGGAAAAATTAATTAGAAAAAAGTTATAAAATACTTCACTAA GAAAATAAAATGTCAGGAAGCCCACTTAGACAATGAGTGAAAATGAAAACAAATTCAAGTT TTTACAATATTTGGTTTCTATAGGATTGCTTCATTGTTTTTGGTTTTTTCCCCATA TTGTTCACATGCCACACAGACAATCAATTATGAAGAAAGGAGAGACTCGTAGGAGGCAGG GCCAGGCTGTTCACACTTTTAAACTAGGTAGCCACAAATGAGGCTTAGTTACAAAAACTT GAAAACTGGATTCTTCCCAATGTATTATACATCCCCAAAGAAATGATGAAGTTCCTTACT TAGGTTTTCATATTGGCTTAGATTTTTTTTTTTCATTAACTTGCAATTTGTGGTTGGGAAAT GATCTGCTTTTTGTTTCAGGTTGTTTAATGTTTTCCAATGTAATATTCTTCTTGCACTCC AGTGAGTTTATTTACAAAACATTTAATGTCATTTGCGTCTTCGAAGAACAATGTATTCGG TTAGAACAAAAGTGAGCTCCTGCATAGAGCTTATGATGGTTTATAATTGGTAAATTATTA CTCATTCAAAGGGACCGTTCACCCACAAAATGCCTTTTTGTTTATCTTTTGGAATGACAC CATTGGAAACTCAGTATGGCCACTTTTATGGTAATAATAAAAGTCATATATAAAAAGGAT CTTTAAACTACTAAATACAAATAAATTAGTAGTACAGTCATTAGGATTGCTCTTAGTTTG TTAGTGTTGGAATAGACTTTTGGATTTTCTTCCTAGCTTAGATTGATACAATGTGATGGG GACTTGCTCTCCAAACACAGGAATAGGTGGCCTGCAGACACACTCTGTGATGCTGTAATT CTAATCCTCACTGAATATCAGGGGTGGACATCTGGCCTGGGGCAATTCAGATACTTTT TCTTAAAATTTATACTACAAATTCAAAAGTGGTAACTCATCTCTGCCATCACTTATAGTA

FIG. 1R

19/51

TGGAGAATAAAATAAGTAAATTAGAACAGGAAAAATGCCAAAACACACAGACATGACCCT GATAGTTTTCCATTTCCTGATCACTGTCCCTTCCTGTGGCTGGATAAGGAACTGTCTCTA GGCTCTGTAAGACATATTTGCATCCTTACGACAAATTTCTACTCCTTTTCATAAACTAGA CTTGGGTTCTTTAACTTGCAACAGCAACAACAATAAACGATTTTGTTGGGTACAATCTGA TTTTATTAACTTCTGGATTTAAAAGCCCTTCTAAATGTTGATTGGCATTGTTTTTACTTC $\tt CTAAGAGTACGCTCATGCACCACATAGTGATGTTTTGGTCAACGACAGACTGCATTTACG$ ACTGTGGTCCCATAAGATTATAATACCATGCTTTTCTGTACTTTTCTATGTTTAGATATG TTCAGATACACAAATGCTTATCATTGTGTTATAATTGCCTACAGTGTTCAGTACAGTTAC ATGCTGTACAGGTTTATAGCCTAGGAGCAATTGGCTATACCCTATAGCCTAGGTGTGTAG TAGGCTATACCATTAGATTTGTGTAAGCATACCCTATGATGTTTGCACAATGATGAAATC AGAAGTACAATAACTTTCAAATCCTGAATGTTCTGTACTTTCCATCTCACAAGCATTTTG CAAAGCATCAAATGGTATAAGCCAGATTACTGTTAAGGCAACTTGGAATTAATATGCTGC TCAGTTCTGGAAAAGGCATATTCTGTAAATATAGATGAGAGAATATAGACTTTTTCCCTC TCTTCTTACAATCCACATTCTATTCAGTATTTCATTTACTTGAGGGGTTATATGCTACTT ATCTTTATCTGTTGTGGAGTGAGGACACATTCCAAATGCCTTGGTATTATTAAAAGCCCT TCATGATGTGGCCCCATCTTTATGACTTTTCCTTTTCAACTGTGCCCTCTAGCCTTATT TGATTTCTCTCAAATTCTTAAACACAGCATGCTTCACTGACCTTTAAGCCTTTGCACATA CAGTGTTGATGTGGAGCTTCCTGACCAACTCCTAATTCTCCTTCAGGCCTCAATTTAAAC ATCACTTCCTCTGGGAAGCTTTCTATTATTCCCAAGGTACTGGGATATGTTCTTGCACAG CATGCTGGGCTAATGTCACAATGGCTACCTTGTTTATTGTTAGTATTTGATCAGCGACA CCTTGCCAGGGAGCCCCTGAGTATTGTCTGAGCAGAAACTATGGCTATCTTGTCCCCTGT ATATCTCAAGATCATGCTGAAAAGCCAGCATTCATGAACAAATTCCTGTGCGAAGATTGA GAATGAAAGATGAATAAGAGGTATCTTTAGAACCCAATTATGGCTGCCGTTGTTCCCTGA GTGTGAGGCTTGCTGTTAGAGTGACAGAAGGAATTTTGACTACTCAAGACCATACAAATT TGGAAATGACTCCAAAGTAAACATGGTTAGATAACTACACATTCCATTCCCCCTTTTTTA TTTCTATAGAATCCCAACTTTGTTCAAGTAGTAACATGCCCAGCTTCAGAAATGAGTCAT GATTTTTCTAAAGCAACAATATCAATCTTCTTTCCCTTCCCCAGTGATTGGTATGGAAGT $\tt TTTTGCTTTCTGCTGTAAATCAAAAGCAGAAACAGGAGAAGATTCTTTTGGGCCTCTTTC$ CCTCTTCCTGGCGTGGAAGTAGTTGTGAGAGCATATGATACCCAAAGTTTCGGTAGACAT TTTATAATTATGTGATGAATAACCTAAGGATAATTAAACATATAAAAGAATGGAGAAAGA CTGAGTCTGTTTTACTCCACAAGATGCTGAACCAACCCTGAGACATAATTTATCTGGATT GATTAAGTGATGTTATCTTCCTTTAAGGCAATCAAAATGCATCTGACAAATGGCCATCTA ATTTAAAATTCCAACTATGTAGACATCTCAAACAAAGTCAGTATCTCAAAAAATATACTA CAAAAATTCTCATGTGTCCATTGGGGATAACTTCCAATGCTCTTTCATTGGTATTGTAGC TATGGCATTTGATTTCCAATTGTATGTGGATCAGGTAGTTGCAGGGTGACTCTCAAGGGC AACAAGACAAAGTCAAACCCTAGGTAGAAATAAGAAGGAGCTAGTACAGAAAGCAAATGC CTAAGGTGTTGGAGAACATAGAAAGGTAGAGTGGAATGAAAAAAGAAAAAACACTAAATA GCAGCACATAGAATCTTGGGGTTTCAGGGATATTGTTTATGAAAGGTTAGAATAGGCAAC AATTACCTGTCATATGGGTCTTGTCATTTATTATAATTTAAGGAGAATTAAAACTGAAC TAGTTGCTGGGGAGTGACATCAGCAAGATGGAGATATAGAAATCTTCAGGACCTCCTTCC GTCCATGGAACCACTGACTCAAAAATGACAAATGGAAAAAATTTACTTTCTGAGAAATCA AGAAGCCAGTTAAGAGGCTCCTGTATCTCAGATGAGTGCAAAGCCAGCTGCAACAGAGCC AGCAGAAAATTTGTTGTACTCACTCTTCATGGTCACTTCTGGCATAGCACAGTGCAATCT AGAAGAAATTCTCGGCTCCTGACTACTTTCTTGGAAAAGAAAAGAGAAAAATGTACCATAT GTCTAATATTCTGATGGGGATGGGGTGTGGGCTGCTCAAAGGACTAGCTTCCGTCATGCC TAAATACAAGTGCTAATTGGGAAGTCCACAATGTTGGGGGCTGCAGAAAACAAGGGCAAC AGTTTGGACTAGCATGCACTCATTTGCCGCAGTTCCTCCTCTCACTTCATAGAATGAGTA GAAGAACCCTTAACTCTCAAGGTTTTTTTCCTGGGGAGAGAAAGAGTCAAAGCAATTATA

FIG. 1S

20/51

ACCAATCTCAGAGTGCAGATGGAACCTAGCATATTCTAGATGCCTGGGGGCCATTGAGAA CAAAAGAGAGCTAGGCAACTTTCAGCAGCTCCAGAAGAACTGTGGTACCACAGATAGACA AGAATTTACACACACTGGTACAGATAAGATGAATTTGCAAAAAAAGAATAGAGGCCCCAG AATTTCTAGCTGGGTTTTTTGGTGAAGGCCTTTCTCTGTATCAAGCTAGTCCCTAAAGAC TGGGTGAGGTGGTTTTTGTTTGTTTTACATTTTTAAAAGATGGGGATCTCACTTT GTCACCCAGACTTGAGTGCAGTGATGCAATCATAACTCACTGCAGCCTCAAACTCCAAGG GTCAAGTGATCTTTCCACCTCAGCCTCCTGAGTAGCTGAGACTAGAGACACATGCCACTG TGCTTGATTAATTTTTTTTTTTTTTTTTTTTTTTTGTAGAGATGTGGTCTCACTTTGTTGT TCAGGCTGGACTTGAACTATTGACTTCAAGGGATCCTCCTGACTCAGCCTCCCAAATCAT TGGGATTACAGGCATGAGCCACCATGCCTGACCTGTTTTGTTTTGTTTTAAAAAACTCAG AAAAATTTCAAAATAGCAATTATAAAGACAATGAGCTTAGAAAACCAATTAATGGACAAA ATATGATAACCAAATTGAATATTACATTAGAGGAGTTTAATACTAGATTTGAACAAGCAG AAGAAGACTAAAAAAGAGTGAAGAAACCCTAAGGACATCATCAAGTAGACCAATATGTGT TATCAGAGTTTTAGAAGAAAAAGACAGAAAAATAGGCATAAAGCATCATTGACAAAATAA TGACCCAAAACCTCCCAATTATGAAAGACAATAGATATTCTGAATCCAGAGCACAATGGC CTGCAACTAAGATGAACCCAGAAAAGTCTATACTTCAGCACATTATAATCTAATTATCAA CAAGGGCTGTCATGAGAATATCAGCAGATTTCTCAGCAGAAAACTTGCAAAACAGAAATA AGTGGGATTACATATTCAAAGAGCTGAAAAAAAGTCTGCCAACAAAAAATCCTTTATCCA GAAGAATTTTCTTCAAAATGAAGGAGAATAAAGGATATTCCAGATAAACAAAAGCCAAGG GAATCCATCACAATTAAACCTGCCTTACAAGAAATGCTAAATGAAGTTGTTCAAGTTGAA ATAAAAGAACGCTGAACAGCAACACAAAAGCATATAAAAGTATAAAGCTCATTGGTCAAA GATAGATATAAAGGAAAAACAACGGGATATTATAATGGTGGTGGTAACTTACTCTTCAT CCTGGTATAGAAGTTAAAAAAAACCACAAGTATTAAAATAACTGTAACTATAAAATTATT AATGAATACACAATGTAAAAATATGTAATTTGTGATACTGATAACATACCATGTGTGGAG GGGAGAAGTCAAAGTGTAGAGTTTTAAATAAGACTGAGGTTAGGTTTTTATCACCTTAAA ATAGATTGTTATAATATGTTTGATTTAAGCCCCATGGCAACTACAAAGAAAATACCTACA GGTAATAAACAAAAGAAAATGAGAAAGAAATGAAAGTGTGTCTCAGTCCATTTTTATTTT TTCTGGAGGCTGTGAAGTTCAAGACTGAGTTGCTGCCTCTGTTGAGGGGCCTTCTTATTG CATCATAACATGGCAGAAGGCATCACATGACAAAAAAAGCAACAGCAAGAGCCAAACTGGC TTTTATCATAGGCCTAGTTTGTGACACCTTACATAGTCCTATGAAAACCCATTAAGCCAT TAGCCCATTAATCCATTAATTCATGAATAGATTAATACATCCATGTGGGGAAAGCCCTCA TGACTCAAACCTTTCTCAAAAAACCCATCTCTTAATACTGTTACATTAGTATTAAGTTTT AACATGAGTTTCAGAGTCTAGAAATATTCACACCATAGCCTTTCACCCCATGACCTCCCAT AATTTATGTCCTTATCATATGCAAATACCTTCATTCCATTCCCGTAGCCCCGAAGTCTTA ACCTGTTCTAGCACCAACTCTAAAATACGAAGTCAAGAGTCTCATCTGAGACTCAAGGCA TGATCCATCCTTGGGCAGGTTCCCTTTCAGTTGTGAAATCAAAACAAGTCATAATTCT AAAATACAGTGCTGGTACAGGAATAAGACAGACATTCCCTTGTCGAAAGGGAAAATAAAC TAGAAGAAGGGGTTAATGGTCCCCAAGCAAGTCTTTAACACAGCAGGGCACATATTAAAT TGTAAAGCTAAAGAATACTCTTTTTTGGGTCCATGTTAAGCATTCTCTGCACAATGTGGG GAACACATTGAGCCACTCTGCCCCTATGGCTTTGCTGTGCTCAGAACACACTTCAGCTTT CTCAGATTGGAATTGCTCATTGGTGCCTGCAGCTTTCCCAGGTGGGCACTGCACACTGCT GGTGTTTCTATAATTCTAGGATCTCAAAGGCAGCTCTGGCTCTCACCCCGTATTTTTACT CAACATTGCTGTAGTGGGGCTCTCAGCCATGGCTCTGTCCCTGTGACAAGTCTCTGCCTG GGTCCCCATGCTTTTAGATACATCCTCTGAAGTCTAGGTGAAGGCCATAGTGGCCCTACA ACTCTTGCATTCTGTATCCCTGCAGAATTAGCACCAGGTGGACACTGCCAAGGCTTATGG CTTTTGCTTTCTGGAGCAGTGAGGTAAGCTACACTTGGAGCCTCTTGAGCCAGTTGGAGT GGCTGAGGAATGATGCGCTCACATGAAGGGAGCAGAGGAGTCCTGAGCAGCCCTGGGCAG CAAGCTGTGGAGAGTACCCTGGGCCTGTCCCCTGAAACTATTCTACCCTCCTTGGCCCCT GGGCTTTTCATGAGAGGGGGCAGTCTTAAAAATATGCAAAATACTTTTCAAACATTCTCC TCATTGTCTTAATGAATAACATCTGACTCCCTTCTATCAGTGCTAATCTCTTTAGCAAGC AGTTTTGCTGTTTACATGGCTAAGCAAGCTGCAAACTTTTCAAATCATTTTGCTGTGATT CCCTTTAATTATACATCTGTCTTTAAGTCATGTTTTTGCTCCTGAATTGGCCAAAAGTAA

FIG. 1T

21/51

CCACACAGCCAAAAGTAGCCAAACAGCATCATGAATGCTTTGCTCCTTAAAAATTTCTTC TATAAGATATTTTACTTTATTATTGTCAAGTCTGGCCTTCTACACAGCCCTAGAGTATGG ACACAGTTCCAGTAAGCTTTTTGCTACTTTATACCAAGTATGACCTTTATTCCAGGTTCT GATACCTTGTTCCCCCTTTCTGTCTGAAACCTCATAACGGCCTTCATTGTCTATATGTTT ACTAGTATTTTGGCCATAATCACTTAAATAATTTATAAAATGATTCAGACTTTCCCTAGT CTTCTCATCCTCTGATCCTTCACCAGAAGCACCCTTAACACTCTATTTACAGCAATATAA GATTTTTTTTGCCTGCTCCAAACCCTTCCAGCCTTTGTCCATTACCCATTTCCAAAG CCACTTGCACATTTTTAGGTTGAGCATCAGCCTCACTTCTTGTTACCAAAGCCTGTATTA GGGTTCTCCAGAGAGACAAAACCAATGGGATATACAGAAGGGGATTTGTTAGGGAAATTG GCTCACACAGTTATGGAGACTGAAAAGACCAAGGTCAAGGGGACGTATCTGGTGAGAACC TTCTCATTGTATCATAACATGGCAGATGGCATCACATGCTAAAAGAGCAAGAACAATAGC CAAACTGGATTTTATAACAGACCCACTCTTGACGACTATCCTATTCCTGTGATAAGCCAT TAATCTGTGAATCCATGAGTAAATTAATCTATTCATGAGGGCTCTGCCTCTATTGTCCCT TAAAGGCCCCACTTCTTAATACTGTTACATTGGGGATGAAGTTTCAATATGGGTTTCAGA GGAGACAAACATTCAAACCATAGTGATGTCACTACAAAAAATTAATGAAACACAAAGGA GTACAGTAAGAGAGCAAAATACAGATAAAAGTGCTATATGATATAGAAAAACAATAAAA TGGCAATAGTAGGAGTTTATCTGTCAGTAGTTACTTTAGCCATAAATGAACTAAACTCAA ACAAAAGACAAAGATTAGCTGACTGGATTTAAAAAATACTATATGCTGTCTACAAGAAGT ACAAGGAGCCCACTCCAAATTTGTAGACACACATAGGATAAAATTAAAAGGATGGAAGAA AGTATTCCATGTGAATGGTAACCAGATGAGAGCAGGGCTCATTATACTTATATCGGACAA ATAAATTGTAAGTCAATAATTGTCACAAGGAACAAAGAAGGACAATATGTAATATTAAAA GAGTCAATTCACCAGAAAGATATAACAATTTTAAACATATATGTATTCAATCTTAGGGCT TTAAAATATATAAACAAATATTAATGGAACTGAAGGGAGAAAGACAGCAATACAACAATA GTAGGAGATTTTAATTCTCAGCTTTCTTTTTCTAGAGACAGAGTCTCACTCTGTCACTCA GGCTGGAGGGCAATGGTACAATCTCAGCTCACTGCAATCTCCACTTCCCAGACTCAAGTG ATTCTCCCACTTCAGCCTGCTGAGTAGCTGGGACTGCAGACATGCAACACCATACCCAGC TAATTTTTTAACTTTTTGTACAGATGAAGTCTCGTATATTGCCCAGCTGGTCTTAAACTC TTGGGCTCAAGTGATCCTTCACCTGGGCCTCCCAAAGTGCTGGGATTATAGGCATGAGCC ATGCTGTGTCACAAAACATGTTTTAACAAATTTAAAAAATACAGAAATCATATCAAATATC TTTTCTGAACACAGTGGAATGAAACTATAAATCAATTATAAAAGGAAACTGGCAATTTCA CCAATATGTGTACATTAAACAATAAATTCTTGAACAGTCCATGAGTCAAAGAAGAAATTA TAAGGGATATTTGAAATGTTTCAAGATAAATGAAAATGTCTCAAGATGAAATAAAAAGAC AACATATCCAAATTTATGGAATGCAACAAAAGTGGCAAGAGTTAAGTTTATAGTGGTAAG TGACTACATTATAAAAGAAAAAAGATTTTAAGTAAACAACCTAACTTTACACCTCAGAAG CTTTTTAAAGATCAATAAAATTTACAAACCTTTGGCTAGAATAACTAAGAAAAAAGAGAG AAGACTCATAAATAATATTGTAAATAAAAAAGGAGCTATTGCAATCAAAGAGGCAGGAAC AATAAAGATTTTCAGGCTATTCTGTATAATTATACACTAACAAATTGGATAACCTAGAAG AAATGTATAAATTCTCAGAAATACACAACCTACCAAGACTGAATCAAGAAGAAATACAGA ATCTGAACAGATCTGTAACTAGTAAGGAGATTAAATCAATGATCAGAAACTTCCCAAAAA AGAAAATCCCAGGATCAGAAAACTTCACTGGAGAATTCTGCCAACATTTAATAGAAAAAA AAATGCCAATTCTTCTCAAACTTTTGCAAAAATTGAAGAGGACGAAGCATTTCAAACTC ATTTTATGAGTCCAGCATTTTCCTGATACCAAAATGAGATAAAGATATTACAACGAACAC ACACACTTTCAAACAAGCTACAGGCCACTATCTCTGATGAATGTAAATGCAAAAGTTGTC AATAAAAAATAGCAAACTGAATTCAACAGTGCATTAAAAGGATCACACACTGTGACCAAG CTATATTAACAGAACAAGGGATAAGATCACATGATAATCTCTATAAATGCTGAACAATCA TTTGACAAAGTTTAATACCCTTTCGTAATAAAAATACTCAACAAACTATGAATAGAAGGC ATGTACCTCAACACAATAATAAAGGTCACATATCAAAAGCTAACAGATAACATCATACTC AATGGTAAAAACTGAAAGCTTTTCCTCCAAGATCAGGAACTAGGTAAGAATGTCCATTCT TGCCATTTCTCATCAACGTATTACTAGAAGTCTTTGCTAGAACAATTATGCAAGAATAAG AAATAAAAAGCACTGAAATCAGCAAGGAAGAGGGAAAATTATCTCTATTCCCAGATATAA TAATCTTATATGTAGAAAATTCTAAAAATCACACAAGGAAACTGTTGCAACTAGTAAGTT

FIG. 1U

22/51

CATCAAAATTGCAGAACATAAAATCGAAATGCAAAAATCAGTTATGTTTCTATACAATAG CAGCAAACTCTCTGAAAAAGACATTACAATCCCACTTACAATATTATCAAAAATGACTAA AATGTTTAGTAATAAGCTTAACCAAGGAGGCTAACGACTTATACACTGAAAACCATAAAA GCATTACCAAAAAATAATTTTAAAAGACACAAATAAATAGAAAGATAATTCTGTTTTCAT GGGTTAGAAAACTCGATATTGTTAAAATGTGCACACTGCTGAAAGCAATTTATAGATCCT CCATGGATACTTAGAAAATCTGGAGAAAGAAGAAGAAGTAGAGGGTCTCATGCTTCCTG ACTTCAAAACATATTCCAAAGCCATTGTAATAGAAACAGTTTAGCACTGGCATAAAGACA AAATAATATACAAAGCACAAAGACTATGGACAGGATAGTCTCTTCAACAATTGTGTTGGG AAAACTAGATAGCCATATTCAAAGGACTGAAATTAGACCCTACTCAAAAAATCAAGTCAA AATGAATTAAAAATTAAAGATCTGGGCCGGGCGTGGTGGCTCACGCCTGTAATCCCAGCA CTTTGGGAGGCCAAGGGGGTCAGATCACGAGGTCAGGAGATCGAGACCATCCTGGCTAAC ACAGTGAAACCCCGTCTCTACTAAAAATACAAAAATTAGCCGGGCGTGGTGGTGGGCGC CTGTAGTCCCAACTACTCAGGAGGCTGAGGCAGGAGAATGGCGTGAACCTCAGAGGCAGA GCTTGCAGTGAGGTGAGATCACGCCACTGCACTCCAGCCTGGGGGACAGAGCAAGACTCC GAGAAAAGTTTTATACCATTGGTTTTGGCAATAATTTCTTGTATACGACACCAAAGAACA GGCAGTAAAAGCAACAAAAAATAGATAAGTGGAACTACATAAAATTAAAAACTGATGCAC AGAAAATAAATAAAAGAAAAAAAACAGAGTGTAAAAGCAAACCATGAAATGGGAGAGAATA TTTGCAAACCATATATCTGATAATGGGTTAGTATTCAAAATATATAAGGAACACCTACAA CTCAATAGCAAAAAACTAACCCAATTAAAAATGGACAATGGACCTGATGGATATCTCTCC AAAGAAGATGTAAAAACAGCCAACAGATACATGAAGAGTGCTTAACATCATTAGTAATTA GGGAAATGCAAACCACATGAGCTATCATCTTACACCTGGTAGGATGACCATTATG AAACAAAGAAAGAGAATTAAAAAAAAAAAGTGTTGAAAGGGATGTGGAGAAACTAGAA CCTTTGTACAGCCACTGTGAAAAAATGTTTGGAAGTTCCTCAAAAAAATTAAAAATAAAA CTATACGATCCAGTAATCCCACTTTTAGATACTTTTCCAAAATATTTGAAAACAGGAACT CAAAGAGATATTTGCACTCTCATGTTTATTGTAGCCTTATTTACAATAGTCAAGAGGTGG AAACAAATGAAATATAATGACAGATGAGTCAATAAAATGTGGCATGTACATATCATGG AATATTATTCAGCATTACAAAAGAAGAAAATCTTATAATATGCTGCAACATAGACAAACC TTGAGGACCTTATACTAAATAAAATAAACCAGTCACAGAATGACAAATACTGCATGAATA TACTTCTATGAAGTATCTAAAGTAGTCAGTCATAGAAGCAGGAAGCAGAACGGCAGCTGC ${\tt CAGGTCCTGGGAGTAAGAGTAAGAGGAAAGTTGCATTTCAGTGGGTATAGAGTTTAAAGC}$ ATGCAAGATGAAAAAGCTCTAAAGATCTGATGTACAATAATATGCATATAATGAACAATA TTGTACTGTTCACTTAAATATGTGTTAGGTCCATGTTATGTGATTTTTACCACATTTTTT TGAAAGCAAGTTGCTAAAGAATTTGCCAAATGGAATTATAGTGACACGAGTTCAAATAAA ATTAAAAAACGAGAAACAGTAGAGTTTACTTAATTTGTTAATATATCCATATTATCATTT TGTTTTAGTTTGTTTCCCATTTTTATGTAGCTAGACTGCCAGTTAATCTCCTAAAATTAT TGGCACCATATTTCCCATTTTTCTGGCTTTTTTATTAGTAACTGGGATCCTTGCAGCTG TATCTATGTGATGCCAAACAATTAGGTTGATCAATTCTGTGACAACAAGCCATCTGGTTA CTTTAGTGAATAGGCCCTTACTTACCTTTCATAAGTTGATTCTATTCTCCTTTGTGCCTT CTCTTTAAATTACCATTATCCTGTAACCATAAATTAAAAATACAGCATCGCTTTTAAAAC GACCCTAATTAGCATTTAGGAACAACTACACTTGCAAAATTATTTTCGATTGGTAGAGG GAAGAAAAGGGTCTTTTTATTACTATGTATTTGTAATTACTTTTTGTCACTTATGTTATTC TTGTGTCTAAATTCAACTCTAGATTTATTCTCTGTTGATATTTTTTATCACTTGAGAATA TTTTAGTTTTTCAACCTCTATATGGCGGGCTATCACTCCAAATTTAGGTTAAACTGTAGG AGTAGTTATATTTCAGTACTTCTTTTACCTAATCAGCCATTTTAAAAATAATTTTGTTCAT GGCAGCAATCTGCATGACAAATTTCTACTTAATAAGCAATGAAATAGTTGGATAAATGTG TATTTCTACATGGGTGAATTTCCCAAAATTCACACTTCAAAGACAGTTGCTGACATTTTT TCAATGAGAGATTTTATTAGATAATGAGTCATCTTAGAGTTATCTTGTAAGTATTCTTTA TGTTTTATAAACATTAGAAATTAAATAGGACTACCATATGGTCTAGCAATCACACTTCTG GGTATATATCCAAAGAAAATCAGTTCAGTATGTCAAAGAGATGTTTCGTATTCATTGCAG

FIG. 1V

23/51

CTTTATTCACAATAGCCAAGATATAGAATCAATCTAAGTGCCCATCAATGGATAAACGTA GAAAACATGGGCTGGGTGCGTGGCTCACGCCTGTAATCGCAGCACTTTGGGAGGCCGAG GCGGGCAGATCACGAGATCAGGAGATCCAGACCATCCTGGCTAACACGGTGAAACCCCAT CTCCACTAAAAAAAATACAAAAAAATTAGCCGGGCATGGTGGTGGGCGCCTGTAGTCC CAGCTACCCGGGAGGCTGAGGCAGGAGAATGGCGTGAACCCGGGAGGCGGAGCTTGCAGT GAGCCGAGGTTGTGCCACTGAACTCCAGCCTGGGCTACAGAACGAGACTCCGTCTCAGTT AAAAAAAAAAAAGGAAAGAAAACGTGGTATATATACACAATGGAATACTATTTAGCCTT TTAAAAGAAGGAAACCCTGTCATTTGCAACAACATGGATGAACCCTGAAAAACATGTTAAG AGGAACAAGTCAGGCACAAATACTTAATGATCTCGCTTATATGTGAAATCTAAAAAAGTT GACTTCATGGAAATATAGAGTAGAATGGTGATTATCGGGTGCTGGGAGTTGGGGTAAGAT GTGGTTGGGGAAACGGTCAAAGAATAAAAATTTCAGTTAAAGAGGAAGAATACATTCAA GAGATCTATTGTACATGTTGAATATAGTTAGTAACAATATTTTGTATCCTCAAATTGCTA AGAGAGTAGATTTTAAGTGTTTTTGACACAAAAACTGATAATTATGTGAGGTAATACATT TTTTAATTAGCTCCCTTTAGCCATTCCACAATGTATACATCTTTTAAAACATCATGTTGT ACATGACAAATATACAATTTTTATTTGTCAACTTAAAAAATATTAAAGATTTAATGTA TCTATGTTTACATAGTATTTCTTTGTCTCCATTAGTGTGTTATACAAATACCCAACTAGA AACATGACTTTACAAATGGTGTATCTGATCTTTTATGTCCCTAGTTATTATTTTAGCCCT GTCTTTTTTTTAATAAAACATATTCTGCTTTTTCTTGTCCTCATCCTTCTATGAGTTGA ATTAGTGACTCTACTCCAAAGTAATGGTGTTGCTTTCTCAGACCATATGGTGATACAAAG GCATATGAGTTATCATAAGCATGGTCTGTGTAGGCAAAGCATGTAACTCCACAAATGCTT CTTGAGAGATTCTAATATAATCTGTGCCAGACCTGCACAAGGCATAGAGAATAAAAATTT GCACCCCACACAGTCACTCCTCATTCATTCATTCAACAATAATCAAGTACCTGGTAATGC TAATGCAGTGTACTATAATTCCATATACATAAACTAATATTTTTAAGATACATGAAGGTT ATGTTATAACTAATAGTCAATGTATTTTTAAAATTACTGTAATCAAATTGTAATTGTAAT TAAGTATTTCTTAATCAACAGAAACTAAAAGTATAATTTCCATCAACTCCTTTTAAGTA TAAATGTAATTAAATGCCTGGCACATTCTTCACATTATATAAGGATCTTTATACTTAAGA CATTTGGGAAACCCTACTTAGGCTTATCATTGACAAAACATTTTCAAAATCTTTTCATTT GGTCCTCACCACAATACTGTTAAAAAGACAGCCTAAGCTGTTTTGTGCTTCCTCCCTAGT TGGGCATCCCTGTGCAATGAGAGGGACAAACAAGGTGGTTTTAAGGTCAGAAACATCCAA TTGCAGCATCATTGGGAAATTTGTAAGAGCAGCTTTTATAAAATGTCACCAACTCATGTA TCTTTAAAAGATGTGCTGAATCTTATGCCTTGAGATTTTTCTTAGTTTCCTTATTTTCTA TTCCCCTCCCACTTTCTCTTTGTCCCTTGGTGGCTTCATTAATCCCATATTACAATACAA AGTAAATAATAGTGCTCTGAAGTGCTTCCTATTTGTTCAGGATGAAGTCTGAAAAATGAA ACTGCAATTTTTTTTTTTTTGAGACAAAGTCTCACTCTGTTGCCCAGGCTGGAGTGCAAT GGTACCATTTCAGCTCACTGCAACCTCCGACTCCCAAGTTCAAGTGATTCTCCTGCCTCA TCCTCCCCAGTACCTGGGATTACAGGCATGCACCACCACGCCTGGCTAATTTTTGTATTT TTAGTAGAGATGGGGTTTCACCATGTTGGCCAGGGTGGTCTCGAGCTCCTAACCTCAGAT GATCTGCACACCTTGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACTGAGCCCTG CCAAAAACTGCAATTTTATCTTAGGGGACAGGTAAGCATAAAAACATCCAAAATCATGTA TTTTTTTTTGAGACAGAGTCTGGCTCTGTCGCCCAGGCCTGGAGTGCAGTGGTGAGATCT CGGCTCACTGAAAGCTCCGCCTCCCGGGTTCACACCATTCTCCTGCCTCAGCCTCCCGAG TAGCTGGGACTACAGGTGCCCGCCACCACGCCCGGCTAATTGTGATTCTTTACATTATCA AAGAATTCATGAAAACAGGATATGAAGATTAGTGAAGGATTCTTTTCATTAGCAAAGTAA CTTTTCTTATTTCAAATTTAACACATCTATTTATAAAAGTTATAGAATTTAAAATTTTAAA ATATGAATGAAGAAAAACAAAATCAGCATAACATAGTAATACATAATTGATATGTACT ATGTGTTACAGTTAGGGCTTAGAAAGATTTAAGCACCTAGCCAAAATTATGCATTATGTT TCAATGGGTTATTTTGATTACTTTTTCCATTACTCCCAAGTGGTCAGGATTAGTTTTAGA TTATTTAAGTAGGTTGGCTGAGTTCACAAAAGCTATTACTATGGGGACCTTAATTGAAAT GTGTGTTTGCACACATAAAAACCTGTTCTAATTTTATGCAACATGGAAAGCATTAATGTT TAACATGTATGTTTGAACAGGGAATTTTGTACTGCATTAAAGATTATTCCTGTGTATTAC ATACAATCAAATATTTGACTATTGACTGTCTTAGTATGTTCATCTAATTGTTTCCTATTC CCATGAAAACTGTATCAGTCTGAGAACAGCTACTATATGATATGCATCACTAGTCTCCCC

FIG. 1W

24/51

ATGGTGCATAATACTTGATATAAATTAGATGCTGTTGGTTATACTTGGCGGGGGGAAAGG GGACACTAAAAAGGAAGAGTCAATTTCTACTGTGAACAAAGCAAAAAGCAAAAGGAGAGA TAAATGGAATTAAATTAAAAATGAAATTGAGAGTGTAGATAAATCTATGTAATGAAGATG CTAGTAACATAGGAAGAGAAATAAGATAGGGTATAACAGTGATTATTTTTCCTAATAAGT AGTGTCATGGCAGTTGGAAGACAAGAGATTATCCAAGCACTGGTTATAGTCTGAAAGATG AGTCAATTAAGACTTATACAAATGCAGAAGTCATGGTTGAGGTAGTGAGAGGATTTCCAG GACAGTGATGAATAACAGAACCTCAGCAGAAGGAGCATGTGGACCCAAAGCATCATACGA ATAATGATAGGACCAAGGGAAAAGAAGTCAAGCGGAATGGGGATAGACAAAAGTTTTGAA ATTTATGTGTAAGAGTTGAATGAAGAAGTTATTAATAAGACTTACACAACAAAGAATTT TAAATTTTAATATGTAATATTGTAGGATTTGAATACCTTAAAGCTGAAATTCAGTTTTTG ATGCTGCTTCTTAGCATCTTTGTCTTGACATGTATATCAAAATGTAAGAATGTCTGTATC ATATCCAATAACATGCCCCAATGTTTCACAGGTATCACACCAATAGCCCCTGAGATATTG TCACATTCCATTTATCTGCAGAAGTCTTATTCAACTTTCTGTATTAAGTACCAAGAAATT TCTTAGGCAATTAGTAAGTTCACTTGTATTCTTAAAACTTCACAGAATGAAAAATTAAAA ATTTTAATCTCTTTTTCTAGAACAATTGTTTTACAAAGACTTTTCAAGGTTTTTTAATCC TATTTTTTGACAAATAACATATTTTAATGAAAGTAAACATGTAGAAATGACTTAACCAA AACTAGCTATTGACAACTTTTCAGCACTTTTTTTTTGGGTGAATTCAGGAACAAACTTTGT ATTCATTTATTAATCCACTAAGTAGGGTTGCTTCACTTCCTTGGTTACTGTGCATGTGG ACGAGGCTGATTTTCATGGTGGGATGTTAAAAGGAGGGATTTTTGCAAATCAAACCACAG AACCATCACCTCACACTTGTTAGGATAACAAACATTAGCAAAACCAAAGATGACAAATGC TAGCAAGGATGTGGAGAAATTGGAACTCCTGTATATGCTGACAGAAATATAAAATGATGC AGCCACTATAAAAATTTTTTGTTTTTGAGAATGTGTCTTGCTATGTTGTCCAAGCTGGCA TCAAACTCCAAGACTCAAGTGATCCTTTCACCTCAGCCTCCTGAAGAGCTGGAACTATAG GCATGAACCACTGTGCTGGCTTGGAATATTTTTATTTTCCTCAAAAAATCAAAAATAGAA TCACCATATGAGCCAGCAATTCCATTTTTGGGTATATATCCAAAATAATTTAAATCAAAA TGTTGAAGAGATATCTGCACTCTCACATTCATTGCAGTAGTCTTCACAAAACAACCTAAA TGTCCATCCATGGATTAATGGGTAAAGAAAATATGGTCTACACATACAATGGAATATTAT TCAGCCTTAAAAAAGAAGGGTATCTTTCTGAATGCAACATCATAGATGAACCTGCAGGAC GTTATGCTAGGTGGAATAAGCCAGGTATAGAAGGACAATTATTGCATGATTCTACTTACA TTAGGTATTTGAAATAGTCAAACTCATGGAAACAGAGACTAGAATGGTAGTTGCCAGGGG CTGGGAGGAGGCAGAAATGAGGAACTGCTGTCCAATGAGTATGTAGTTTGAATTATGAAA AAATGAATAGGTTCTAGAGATCTGCTGTACAACATTGTGCCTACAGTTAATGATGCAGTA TTATGCACTTAAACATTTATCAAGAGAGAGATGCCATGTTGAGTGCTCTTTTCACAATG AAAACTACTTGGGAAACAAAATGGAAGGTCCCCAGAGTCGTGAGGGAAGTAAGGTATGGT TCTCATGCCTTAATTATAGTTTACTGCTGAGATAATTGAGAATGAGAGCTCATATTTACT AACCAGGATATGAATAGACTGAGAACTTTAAATAACTTTCCTTTAATTCCATAAAAATCT CCATTCTGTTTTAAAGTCTTTAGTACAGATTTTAGATGTAATAAACTGCTAAGATTTGAG CAACAACTATAAGCATAATAAATGGTTTGCTTTATGGGCAGTTTTACACTAATGCCTCTA ATAATAATAACAGTAGCAATAACAAAAATGACAGGATTCTTAGGACTTCATTACTCAGAG CATAATCCCTAGAAAGCAGCAGTCATTATCTAACCCAGAAACTCCCAAGAGTTTGCTTAA CACTTTAAAATGTATAATCTAAATTAAAGAAAATATGAGTAAATGGTATTGTTTCCCCTG AATTGAAGTAATATGGGATGTGTTGAAAGAATACATCAAGACATTTTTCACTGTCACCTA GCCTGATGACTGACATAGATTAATTACTACATAAATTTCCTCTTCCATTTAATACTGATA AACAGATTTATGGGACTTAAACCACAGTACACAGTTTTGTATTTTGTACGAAATGGATAA TCACATTTTAAAACATGTGTAAGGCATATTTGCAAACTTGAAACGTCGTCTTCCATAAAT ATATGCTGAATGAATGAATTAATGAATAAAAATTGAGGCAAAAACTCAGGTGTGGCTCAG ATTTCTAGCCAATAAGACCAAGGTTCATTCACTTCACCTCTGTATAGAATCCTTTGTTGG GGGCTGCGAGGAGGCAGTAAGAAGTATCACATCTAATCTTTTCCATAATTAGCCAAGTTA GTTGGTACTTCCCATAACTCTGATACCCATAGGCCCTTGCTATTTCTAGACTTGAGTGTC ATTCAGAAATATGGTTTAGGCGAGCACTAGGAAAGATACACAGTTTTTCTAAAACACATT

FIG. 1X

25/51

ACATACAGGTATTCTATTAAAGGAACTTTTTAATGTTTGACCAGAAAAAATTTCAATATC CCTTTTTATTAAGTTTAAGTTACTGTAATGAAATTAAACATGTGAAGGGAGACTAATACT CTCTTTTAAGAGAAGTAAGAATGAAATATCCATATAAAATACACTGCATTATTCTCTTTG AGAAAGCCAAGATTTTATAAAGTAAAAATCTGCTTTGTGTGCCTTTCCAAATTAGAAGAG TTGAGTGAAATAAAAAGAAATTGACTTACTTGTTAAAGAGAAAAGATTGCCAAGGCTTGC ACGTGCCTTCCATTTAATAAATGCTGTATCAATCTAGCTGTTTCTCTATTTTTAATCATA CATTTTGTTGTTGCTCTAAATTTAATCTTACCTTATACATTGTATAATAGATGTCCCTTA CACTCCTCCTGCTGTGATCAGTCTCTCCGTTTTTGTTCATTGTCCATCATCTTCTACAGA ACAGATGTGTCCTAACCCACTTTCCTAAACACATTTTTGTATACAAAATAATTTCCTTTT TTTAATTTCAGAACTCTATTCTGACAAACATTTGGCTTCAACCTGTAATTAAAAACTTAA CAATACTTAATAGTTGCCTCAAAGAGCATCCCCTCTTTGTCAATGTGAGACTATTTACAT TAATTTACATGTAATTCAGTTTCATACTCATTCACTGGGGTGTGAATATTAGTCAAACGG GCAATTAATTAATACAATCTTTATATATTCACTTATTAAAAATGCACCACACAATTCCTAA TTTATTGAGAGTTCTCACTAAATCTATGGGATGTAAATTTTGAAACAGCTGCAGCTGTTT TCCTTGAATAGAGTCGAAATTATGAATCTAACTTTCTCCGACATGTTGTCTAAAAGGATA TCATCTTACCTTACTCAGTGTGAGCCCTAAAACTAGGAAATGTTTATCAATCTCTGATTG CAGATCAAGTTTAACTATCAAATACAGATTAACTTTTCAGCAAAAATTTGTTAAATATTC AGAGATAGAAATCTTGATGTTGGATGACAAAGATCACTTGTGAAGAACTTTATTAAGTTT TATTTGGTTGAAAAATCTATAATTTTTAGTGAACAACTATCATCCATTATGTTCCAAGCT TTGTGACAACTGTTTTTATGTCCATTAAAACAGTCCTATAAAATAGGTACAAGTATCTCA ATCTTATACATGTCAAAACTAAAGCACAGAGATGCTAAATAACTTGACTAAACAAGATAT TGAAGGTGAAGTCTGAGATAGATTTTTAACTCCGAAGTGCATAAACTTTACCTCTATATT ATCTGTCTTCAAAAAGAATGATTTTAAAGATTAGGCTTTTTTATTTCAGAAGAAAATATT AAAGTGAGGTACATTTTAAAGGAAAAGTGACAGACAAAAAATGGATTTTTGAAAAATGAA TAAAGCTGCTTTTTTTTTTTTTGATGGTGTCTTGCTCTGTTGCTCACGCTGGAGTGCAATG GTGCAATCTCAGCTCACTGCAATCTCCGCCTCTCGGATTCTAGTGATTCTCCTGCCTCGG CATCCCGAGTAGCTGGGATTACAGGCGCCCACCACCAGACTCAGCTAATTTTCTGTATTT TTTAGTAAACATGGGGTTTTACCATGTTGGCCAGGCTGGTCTCAAACTCCTGACCTCAGG TGATCCACCCACCTCGGCTTCCCAAAGTGCTGGGATTACCGGCATGAGCCACCACGCATG GCCAAAGCTGGTTTTTAAAAGGGATCATTGTACATTATTATCAAATTTCATTTGAACGTC AAAAATTCTGAGGCAAGAAGGAAATTGAGCCCAGGAGTTTGAGACCAGCCTGGACAAAAT GGCAAGACCCCATCTTTACAAAAACAAAAATAAAATAACACTAGCCAGGCATGGTGGTGC ACACCTATAGTTGTAGCTACTTGGGAAGCTGAGGTGGAAGGATTACTTGAGTACAGAGAA GAGGTTACAATGAGGGAGGATCGTGCCACTGCACTCTAGCCTGGGCAAAAGAGCAAGACC CTGTCTCTAAAGAATAACAAATAAATAAATAAAGTCTGGACAAGCCTAAAATCAGTAATA TTTGGGGAATATGCAAATAGTCTTTGCTTTATTTACTCAATTATTGAAACTATATTCAAA AATAGGAAGTAAAACATGATTTAATATTTTTAGTAAGTTAAACATGTTATAATAATTTT GAAATCCATGTATGTTAGTTAAATATACATTACTATAAAATGTAAATCAGTGTGGTTTGT AGCAGAGACCTGGATTTTTTATCTTTGTAGTGTACCTACACCATCACAGAAAGGTTTGCC CATTCTGTTGTTTTCAGCCTTCATCTAAGACACTCTCAGATACTATTTCAGGAATTTATG ACAGCAAAATGATATAAGGTGACAAAGTAGAAATAGGTGCTATGCTGCTTTACCTATATT GAGTTATTTCTCTCTCCAGGATCAGATATTAATGATAAATTCTCTAACATCAAAAAAT TCTACTATGTTTAGAATGGAACACCTGACTTATAGAAAAAAAGGTAAAAGATTGGTTTTG ATTTTAAAATACGATAAGAAGAGGGGGAGAAATGGCTAGATTAATTTGAGGATTACCTA GTGTTAAAATAAGTCCAGATTTAAATCAAGTTTATTAATTCTGAAAAAGATCACATCCTA

FIG. 1Y

26/51

AAGAAGGCATCAAATTGACCCATAAATGTGGATAAAACTTCTGTAAGATAATGAAAGCCC TAGAGAGTAATGTTCAACTCCATTTTCTAATTGGCAACAAATGTATAATATGGGTACACC AGAATATCTAACTCAAAAAGTGGGGAAAAAAACTCAAAAAGTACGAAATGTTGGCAAAAA TGCAGACAGCTAGGACACTCATACCAGCTGGTAAGTGTAAAAACTAGTACTGCACCAAGC ACTTTAGAAAACTTAACGGCAGTTATGTAGTAATGGTGATCATATGCATACTCTATGATA GCAATTTCACTGTTAGATATATAACTAACAGAAATTTGCACATATGTGTCAGAAGACGTA CATAAGAATGTTAGTAACAGCCCTGTTTACAATAGCCCTGAATTAGAATGAACCAAAATT TCCATCAATTGTAGAGTATTTCAATGATAATATAATCACACACTGGAATGAAAATGATGG ACACAAAATAACACATAAATGTTGATTCCACATAGATAAAGTTAAAAAACAGATAACAATT AATCTATGGTGTTACAAATCAGTATACGGATTTCCTTTTGTTGGCAGGGGGGATGTTGTT GGAGAGGAAATAGGAAGAGAGCTTCTGGGGTGCCGGTCATATTGTACTTCTCAGTCTGAA TAGTAGTTACAAGGGTATGTACACTCTGCTGTAATTTGTCCAGTGATACATGATGGTTTG TACATTTTTATACATGTGTGATAATTCAATAAAAATATCTGAAAAGCTACAACAGCAGTG GCAACAACAAGCCCATTAACCACAAGAAATAATCATGTAAATTGTTTTCTTCAAATAAA TGTGTTGTAAATAACTTCTCTCACTCTTTGGCATATATTTTTGTCCTCTTTTGATATACC CTAATTTTAGGTTTGTTTAATTTTTCAAACATGTCCTTTATGTTTAATACATTTGAGGAA ATCTGCTTAAGAAATGCTTATCTACTCCAACATCTTATCAATGGGAATTTTATTTTTTA ACTGTCAAATTTAGATCTATAAGTAACCTGGAATTTATGTTTGTATATGATGTGATGTAG AAATCAAATTTTTTTTTTTTTTTTTGTAGATATCAATTTATTCAGTATCATTTGTAGAAAA GATACTTCTTTGATAATGCAGTACATGGCACTTTTGTCATATGTCAAGAGTCCTTATATA CGTAGGTGTGGATCTCAACTATTTTTGTTTTGTTTTTGTTTTTGTTTTTGGATCTCAATTTTT ATTCTATTCCCTTGATCTACATTTATATCCTTGTACCAGTACTATACTGTTTTGTTTACT GACACTTTGTATTAATATTTGATAGCTAATGTAAATCCTTCAAATTTGTTTTTCCATAAT ATAATACTGACTAATTTTGGCCCATTATATTTTTATATAAATTTTGAAATCAGCTTGCCA GTCTTTACCAAAGGAAAGCTAGCATTTTAATTTGGAATGCATTGAATCCATATATCAATT TTAGAGAAAACTCACAGCCTTACAATACTTATTCTTCGATTCCATGAGTAGGGTATATCC CCCTATCCATTTAGGTTATTTTCATATTCCTCATATTTTACAGTGCAGAAATCATGTGT TTCTCATTATTTTTTTCCTAGATGTTGAACATTTATTATTCTATTGTCAATAGTATCATC TATTTAAATTGCATTTTCTAGTTGTTTTTTTTTAATAGAAACATAATTGATTTTGCATAT ATACATTATATTATATATCAATTTCATGTGCTCTTATGTTACATATTGTTTTATATTC AGCAAGTGTTACTAAGGTATTTATTAAGATTAGTAGTTTATCTGGAGATTCTTTCACACT ATTTTATTTATTTATTGCTTTATTACCCTTGCTCCAGCACAATGCTAAATAGAAATTA CCATAAAAGACTTTGTGCACTTACTCCTGATCACTGAGGGAAAGACTATTTATGTGAATT AGTATTTGTAGATATTAACTTTTGAGAATTTAGCTGTCAATCCCAATATGACAACTTGGA GGTGATGCATTTTTTCTTCCTGCTTTAAGATTTTTCCTTTCGTCACTGGTTTTTCAGCA GTTTTATGATAATATAAGTGGGTGTGATTTTCTCTTATATTTATCCTGGTTGAAATTTAT AGCACTTCTTATATCTACAAATATATACCTTTAATTCGTTTTGAAAAATTCTTAGATAAT GTATTTGCCTTGCCAATATCTTTTTAAAGATTGCTTTTTGTCTCATGCTACTTCTATACAC ACATATTGAGAATCCAATCACAGGTATAATAGAATTTTCACCATGTGTTATGCACACTCT TCTGCATTTTCCTTTTTCCTCTCTGTTCTTTAGCTTGGATATTTTCTATTAGTTTGTAT AATCCTATTAGATGGTTTTATCTAATCTTTCTTTCTGTTAAATCTCTTTGTTGTTTTCC AGTTCACATATTTTTAAGTTCTATAATTTCCTTGGACTATTTTTCTATTTTTTATATTCT TTATAATATATCTACTTTCTTGACATTATTAATTCAATCATTTTAAAATTTCTGAAATAT ${ t TTTATGAAAATTGTAGAAATTATTTTATGTTCTAGATAATATTATCTTCTTTCACAGAG$ AATTTGCTTTTGCTTTGGCCAGCAGCTAGTGTTGGGACAGAAAACCACTATCCCGTCAGT CACTGGAGGCTTTGGAAGCTGGGCTTCATTCTTTAGGAGAGCTTGTCTACTTCAGATTTA TCCCTATCAGAGTTCATAACTTGGAGTTACAGCTGAAAGCCAGGGTTGTTTACCTACTTG ATAGGCCTTGAACTCCAATTATCATCTTATTTTTGGTTAGGTACTAAATTTCCGGCTCAG CATCTCATATTATCAGCTTTGTTCTCTGTTTCTCTCTGTTCTTAGCTAGAGTTTGC AAATTGCCAAAAACTTTGAGAAGAAAAGAGGCTAAATGCCAGAGCATCTCCCTCTTGCAT TTTCTCCAGGATATTGGCCTTTGATGTCCCTTCTGCCTTAGTAGCTTTCCAATGTCTTAA AGAAATGTGTAACACTTCTGGTTGTTTTAGGTGGGAAGTTTGTTCTGCAGTAAGCTTATC TGCCGTTACCAGAAATAGAAACTATTTTGTAATAGTAAAACAAATGTATACTTTCGTACT ACAATATTTAGTACTTCAGAGAACAATTGGCACTTTCTGGATATTCTCAACCAGGAGTAT GTGGTTGAAACTGCACAGTTTTCTGGAGATGATTTAGGTTCTTCCCTTCTTACTCTAATT

FIG. 1Z

27/51

CTGTCACTGGTTGATCTTATCCACTCCACAAGCTTTAATCACAATTTCTATTCTGATGAA TCCCAAATATTTACATGTAAAGAAATTATATCCCCTGGAGTATAGAACCATAAATCTAAA TGCCAACTGGGTATTGACACTAGGATAACTCACAGGTGCTTCAAAATTACATATACAAAG TTGAATTTCTCATCTTCTATCTACTCTTACAAAGCTACCTCATTATCCTTTATCCCCTAG CTCAGTGAGCATCCCCAGCTGTCAAGCAATATACCTGCTAATCATCCTCAGTTCTTCTTA CTCTCTCATCCTCATATCTAATCCCTCACTAAGGCCTGATATTTCAACCTCGTTATTATT TTTGGCATTCACCTTTTTCCATTTTTTGGTTACCAACTTGCTTTCTTGGAATTTTAAAAC TGTCAGTATTAATCTCTCTGCTTGCAACATAAAGACATATATTTTCCACATATTCCGCCT AAGTAATCTTTGAAAAATAGTAGTAAGATATTGCCATTCTGTTGCTTAAAATCTGTCAGT AATTTTGTAATTTTCCAATTCTCCATAGTCTGTAGGACAATATCCAAATGTTTTAACTGA ATACACACACAGAAACACACACACACGCTCACACACATTTTATGATTCATACTTTGAG TTTAATTGAAAGATAGAACATCTATAAGATGAAAACAGTTGTAGTCAGAGATTCTGGTAT GCAAAGTAGGAGAGAGCCAAGAACTAGAGGTATAACTTTGAATTATAATATTGGGTTG TGAAAGAACAAAGGCAAGTGGATTAAAGACAGATATGCGGTGAAAGAGAAAAGCATTTC TACAGAAAAGACCCCCAAAATAAGTTCATTGCAGGTAGTAAGATGAACAGAAGTCAAATG AAGGACTGACTTTATGGCCCTGTAGAACTCTGAGAACAGGGTCAAAATCCAGATGCATTT CTAAGACATCACACTGGGAACGGGGACTTGTAATGAGTTATCTACAAAGTGTAAAAAAGAT GTGGGTAACCAAAAGGTTGTCATTTCCTCCAAAACAAATTTTCCTGGAGTGAAACTGTAA CTACCAGGTATAGTCATTAATAGAACTGCAGACACTAAGACTATGGAACCTTCCGTCTTC CTAACCTTCTCCTCAGGCCAGCCTTAAAGGCCTGTGAAGATCTATTAATAACACTGCTGT TTTGTTCTCTGGCAGCTCTTGGTGCCAGAAGGCTTGGTGCCAATTTGTGGTTGAGCCCCT CCTTGGGAGAAATCATGCCATTCAGAGACAGCTGATAAGTCAAGCCTATTTTCCCACTTT CTTCACTGTATTTTTCCTGTCTGAAGAACTTGTTTATGGATTTGATTTCTGTAGAGATAA TAATCACAGGATTCAGTGGTATAGCATTCCTCTATGCATTTTCTCCCTGCACATTTGTGT GTGTGAAGATACTCTTTCTAAATCCCTTTCAAGACAAATTATTAATTGTGATATATTAAT TATTCTCCACTGTACCTAACGGTTATCAACACTACAGAGGCACCATTGGTTGACAAAAGT GAGAGCTTTTCTCAACATTAACATAATGAGCAAGTGGCAATGAGAAAATATTTGTCCAAT TAGAGACTTTTATATTTTCTTTTCTTGAGGAAATAAAACCCGAAACACATTTAAGATACA CACTCTGTCGCCCAGGCTGGAGCACAGTGGCACGATCTCGGCTCACTGCAACCCCCGCCT CCCGGGTTCAAGCGATTCTCCCGCCTTAGCCTCCGGAGTAGCTGGGATTACAGGCGCATA CCACCATGCCCAGCTAATTTTTGTATTTTTGTAGAGATGGGGTTTCGCCATGTTGGCCAG GCCGGTCTTGAACACCTGACCGCGGGTGATCCCCCCGCCTCGTTCTCCCAAAGTGCCGGG AGCACTTTGGGAGGCCGAGGCAGGGGGATCACGAGGTCAGAAGATCTAGACCATCCTGGC GGCGCCTGTAGTTCCAGCTACTCAGGAGGCTGAGGCAGGAGAATGGCGTGAACCCGGGAG GCGGAGCTTGCAGTGAGCCGAGATAGTGCCACTGCAGTTCGGCCTGGACGAAAGAGCGAG AGATAACCATTTGGGTGGCACATTTCACAACACAGATGCACTTCTTAAGAGTCCTCCATC CGTCAGCGTTGTAAAAAAGGAAGTGGCACGTTTGCATGTAGTTCTTCTGAGACGGAGATT TAGGGACAACTTTGCCAAGGTGTGTAGGTGGAGAATGGGAGATTGAGACAGGCATATTGG CTCAGGAAGACAAGGGAGTAAAACTAGCAATAGAAAGGAGGGCCAATGCCGTAACAGTGT CTTTTTAAGATAATACTCCTGGTCAGCTTCCCAGGTTCTTAAGTCTGGATACTGTAATGA GTTTTATTTCACGTTCTCTTATTTATATTTAATTGAGATGGTGTTGGCCATTTTATCCTT TACATGTGCACAATGTGCAGGTTAGTTACATATGTATACATGTGCCATGCTGGTGTGCTG $\tt CCCACCCCACAACAGTCCCCAGAGTGTGATGTTCCCCTTCCTGTGTCCATGTGTTCTCAT$ TGTTCAATTCCCACCTATGAGTGAGAATATGCGGTGTTTTGGTTTTTTGTTCTTGCGATAG TAAATATACTCAGTTCTACATTATAAAAAGTATTACAATGAATTTAATGCTTAAAAACTCA

FIG. 1AA

28/51

TTCCGGAAGTGACGATGGAAGCAGGTTCAAATGCTTTCACTGACACTTTGTGGCAAAGTG TGGAACTACAGTATATTTTTCCAAGTTGTTTCCTGATATATTTTTTATGTACATAACAAT CAATAAATTGTTATGTATTTATTTATGTACTTATATGTAAATTAAACAACCAAGAAATC GCAAAGTGTTTTATTAAGATGATATCTAAACTGAAATATCACAACTTACTACAAATAATA CTTTGTTTCAAAAATAATTTGAATTGCATATAAAAATCACAGTTGCTGTGATTAACATTG AATACCATATTTATAAAATGAGTCATTAAGATTATCCCTAGGCATTTTCATTCTGTATTG TCGCCCAGGCTGGAGTGCAGTGGTGAAATCTCGGCTCACTGCAGCCTCCACCTCCCGGGT TCAAGCGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTACAGGCTCCCACCAA GCCCAGCTAATTTTTGTATTTTTAGTAGAGACAGGATTTCACTATGTTGGCCAGTCTGG TCTCGAACTCCTGATCTCAGGGGATCCACCCACCTCGGCCTCCCAAAGTGCTGGGATTAC AGGCATGAGCCACCACTCCCAGTCGGCAACTAATTTTTAAAATTGTGGTAAAATATACAT AATATACAATTCAACAACTTAATCAGTTTTAAGTGTATAGTTCAATGACATTAAGTATAT TCACCTTATAGTGCAACCATCGTCACTATCCACCTCCAGAACATTTAAAATTTTTTAAAA CTGAAACTCTTCACTCATGGAACAATAATGCCTCCTTCCCCTCTTCTCCTAGCCCCTGGG CAAAAAAAAATCTACTTTCTATCTGTCTGATATGATTGCTCTGAGTACCTCATATAAGT GGAATCATGTAATCATTGTCCCTCTCTGTTTTTACCTTATTTTAATATAATCAAAACTAA ATAAATAAGCAAATTCTTAAAATAAAATTGATATTTAGTACAGATCCTTTTGAGACAC TCAGTGGTCCACTAATTATGTACCATATCCAATCACATCACAATATCATAAATTTTATAG TCAATTATTAGTTGGCATTTCAAGGCCCAAGTATATGTTTAATAAGAGACACAATCTTAC ATATGCAGTTTACATGTTTTAATCTAGTCTTAGCACCAGCATATCACCTTAGTTTACAT TTGTCTAAGTGCAAGTATTGGTTTTGGAATGTAATTTTGCTCATATACAATCTGTAAGAT ACTAAAACAAAAGCTAGTTTATTATAAGTGAAATAATGGCAAAGGCCATTTTAAAAATAT TGTATTATTTTCCCATTTGAAAATCAGTTTAGTCTTTAGCCCACAAAATAACAGGAAAAT AACTTAAATCATAAAAACTATATCTGAATATTATTTAACATATTTTATAAAGATATCCTT CTTTGGATCATGGCTGCAGATGTTTTCATGCAGCTTGAGCCACTTTCCATGTCTTACGGA ACAGTCTGAAAGATAAAGGAAAAAAATAATTGATATCTTCTTGGCACCTCTGCATTTCAA AAATACTATTTCAATAAAGTCCATGTTAGAGGTGGAATTCAAGAATTCACTGAATCTGCA TTCTTGCCTTCTGCTATCCTCTTTTGCCCTCATTTGCTCAATTATTCCTCACTCCTGGTT AATGAAGGCAGGCTTTTAAATACAGACTAACCATAAATTGACTTTAATATTGGTGTTTAA TGGTTATTCACAGAACTGATTTAAAATGTGGTATCAAGTTCAGGTCCTGGGATTTACCAA AGTTCATCAGAGGACACAGTACATGGCGAATTGAGAACCATAGCCTACTTTATGTCTAAG AGAATATTGACAAACAGCTAAGTTCTCTGTGAGCTCTCAGATTTCACTCAAAAGAAATGA AGAAAGTAAATTCTCTGTTTAGACTTTGTGCCTTTTTTCTCCTTTTAAAGAATTTGCTCA TCGGAAAATATACCATACCAATGGCAGCAACATACTATAAGTTTATGAGCAAATCAATTC CATCCATAGTTACTGCAGAATGTATTATAGGCAGTATTTTTGTTGGGAGAAAAGCAGCAG AAACTTAGCAAAGTAAGGGAAAGAGAAAAAGCAGCTTATAATGATAAAGAGCCTTTGTGC CCGTAGAGAGATAAGAAAAATACAAAAGAAATCCATAATGATCCACAATAATTTTAGAA TGCAATTTATGGCCATGAAGGGTACAACATGTGATTGGGTATCAAAGAAGAAGAAGTCA TGACCAGTTGATTTTGGACAGTTTTGGATACTATTTAATTGGTTAAAAAGCTATTGAAAT GGAGTATCAACCATTTCCAGACAGAGGAATGGCATGAGTGATGGTCTGGGCACGGAATAT GTTTGACACACAGTGAAATATCAGATTCACTCTGATGCTCTGTGTATTTTACGGGAAACA TTATAAGGGATAAAGGGCAAAAATTCAACAGAAACCCAGTTACTATTGGCCATCTGAGAA TTTTGTACTGTCCAGGAGAAAAGAGAGCTCTCATTGAAATGGAAGAGTTAATACAACAAG ACATTGTGCTTGTCTGTACTCCTATATATTTTATCCATTAAAGGAATTAATGGATTTTAT CCATTTTATGACATTTATTATTTATGACACTTATCCATTAATGACATTAATGGATAAAA CATATAGGAGTACAGACAGGCACGCATGGGGAAACTATTAGGAGGTCACTGCAATAC TATACTTCAGAGAAGCACAAAGTCCAGTGATAAGTTTAAGTTGTATAAATTTAGTGTGCT $\tt CTCAGGAGAAGGTGATGTTTACTTTGTACTTTTACAACCTTGCACGGGTGAGTGGGTTAC$ TGAATAAACAAATAAATGTTTGTGTAACACAAATTTAGAGAATGTGCAGTTGTAGATATA TATGTAGTTCTGAATAGTCCATTTAAAGACAGATACTAGGTTTTCTTCCAGGGTTTCTAG

FIG. 1AB

29/51

AGTTTCGGGTCTTACATTTAAGTCTTTAATCCATCTTCAGTTGCTATTTGTATATGGTGA GAGATATGGGTTTAGTTTTGTTCTTCCGCATATGGCTAATCCAATTTTCCCAGCACCATT TATTGAGTAAGGCGTCCTTCCCCAGTGTCTCTTTTTTGTTGAGTTTGTTGAAGATAAATTG CCTGTAGGTATGTGGTTTTATTTCTGGGTTTTCTATTATGTTCTATTGATCTATATGTCT ATTTTTATACTATTAATAGTATCATGCTGTTTGGGTTACTATAGGCTTATAGCATAATTT GAAGTCAGTTAATACGATACCCACAGCTTTGTTCATTTTGCTTAAGATTCATTTGACTAT TTGGGCATAGCCACAGTCTTTAAATATTTGAATGGACATAATGTGAAAACCACACTTAAG ATATGTTTAAACGGCACAGTAATATTATCTAACACAAACTCAAAATTCAAATGTATCCAG TATATATATATATATATCTTCCCCAAAAGTGTGCCTTGGCTTTTAAAAAAGCTTACAA TCTGAGTAGATTGCACCTGGAGAAATGATTGCAGGTATGGATAGCTCACTTAGAGCTATT ACTGATAATCTGAAGTGTGTTCAGAATAAAATAACCAGGGTGATGGGGAATGAAAAGCCC ATAAGTTTCACATGATGGATTCTGATTATCTTTAGGCTGGAGAAGCATAGGCTAGGGAAG TGGGCATAGCTGTTGTTAAATACTTGAATGAATGCCTTTTTGATTTGAATTGTGTTT CTCCAAAAATATATGATTAAGTCCTAATGATCATTACTCAGAATGTGACCTTATTTGGAA ATGGGGTCATTGCAGATGTAATTTGATATGGTAAAGTCATATTGCAGTAGGGTGGGCCTT TAATCCAATATGACTGGGATCCTTATGAGATGATGGCCATGTGAAGATAGAAACACAGTA GAATGTCATGCACTGACAAAGGCAGAAATTGGAGTTATACTGCACAAGCTAAAGAGCACC AAAGATTGCCTGAAAAACCACAAGAAAATAGGAAGAGCTAAGAAGAACTTTACTACAGCT TTCAGAGACAGGACAGCCTGCTGACACCTTGATTTGAGAGTTCTAGCTCCAGAACTGTG AGACAATAAGTTTGTATTGTTTTAAGACACCAGGCTTATGGTACTTTTTTACAGCAGCCT ATTAGGATCTTGTAAGCAGAAACGAAGGGAAAACAGAACATGAACAAGAACTTGCTAGTA ATTAAAGCCACTGCAAAATGAACTCAAGGGCTCCAGCAGGTTTTAAATTACCTGGTATTA TAAATGTTCAAGCAGGATGAATCAGAGATGGTGCAGAGGTGATTATTCATGCATCAGATG GAAGGTTAGACTGAATAATCTCCAAGTGAAAAAATTATATGATCCTATCTTAAAGCCCTG GATATAGCTTGGTGGATAACACTTAAATTGAAGACCTAGTACTTAGTTTTACTT CTGTTAAACAGAGATATTAATGCTATTCACTTCCTAGTGTTATTATGATGAAACTAGTTA CTTTTGAACATATATTTGCTCTACTATTGTCTAGATTGTCTAGATATAATGCATTAAGTC TTCCCACCAGTGCCATTGCTCGTGTCCAAAATACAGAGTTAAAAGATTAGAAATAATTGC ATGTTTTCTAAGAGTCCTGCGCATTTTCCTAGATCCAATATTGTACTATTTGGACAATTT ATTGACCAAGTACCAGAAATATAATATTTTTGCCAATTTTCTCATAACAAACTGTGATAA CAAGTGTTTATAGAAAATAAATCACTCAATGGCATAATTTTCAAATAATAAAGACTACAG TTACCCTGATTAAGGTTCACCTGAGTTTTGGATATTACCACGTGAGAGTTAGAGGACAAT GTGAAGTTTTCAAAATTAAATCCTCTGAAATCCAGGTATCTTGTTAAATTGACATCTGTT GGTAGCTGACAGCCAATTTCAGCTTCAGGAACTAGTAAGAACATTTTCCAGCTTATGAAA CTATTAATAAATGTTACATAATTGTCCAAAGAAATCCTCATTCAGTGATTCAAATTTAAC AAAATTAGGTTTTATTTATTCGCTATGTAAAGATACTAATCCCTGCATTATTTGGGTGCA TGGGTGACAGCTCTGACAGGTTTGTGATGCCCCAGACAAATTCAGTAACTTTCAGTGAAG CAAACCCATGAATAGATGTGATGGCAGCGTGTACACCTATATAATTCCAGAGCTAGTGAT TATGTAACTTTTATATACGTCAGACCGAAGGAAGACAGAGAATGGAGGAACTGGGTGTTC TTTCAGTAAAGAGCAACTGAATGAGACAGTACATCTTTTGAACTGGGGATATACTACAAG GCAATGAGGGAGGCTGGCTATGAAAAGTATTGAAAAATATGTTTGATTGCTGGGTGATGTT TAGAGGCCCTAAGGTAATAGAAAGGAGACAAAATTGAGAGTCTGGAACTTATATGTACTT TATTACAGTACTCTCATTTTCACCAAAGAAGGCAACCCATGTGGTGAAAAGACCACAAGC ATTGGAGCTAAAGCCAAGTTATAGCTGTAGTTTTATATTTTGTGAGCCCATATGTCCTCA GACAAGTTTCGTGAGTTAATTTCCTTTGTCTCAGCTTCCTCTTTTATAAAATGTGGGTGA TATCATTGTCCCTTAAGATTGTTGTCAGCATTAAACAACATAAGTATATGAACCATCTAG CTCGGTATTTGGCAATGGTAGGAGCTGAATAATTGTTAGCTCTTACCTTAAAAAATTATT

FIG. 1AC

30/51

TGTTAAAAGTTCCAAATGCAGCGTTCAGGAGAAGATATGGGTCAAGGTCATGGATGAGGC AAACACTACAATTCAATAAAAATTGTTAGTTCTTAATTTATCTTAACTCAGCAACCGTTT CTTGAGACTCTACTACATATTGAGTACTGAGGGAATAGAAAGATGAATCAAAGACCATTT TTGAGAAATGTCATGCAAGGTAAATGAACTGATTTTAAGCATGTACTTAGCATTCACACA GATTGACAGATTCAGTGAAAACACGGCACAGCCTTCAATTATTTTTCTTTTTAAATACAT ATTTGTGGACTTTATAGAAATACTGACAGTGTTTCCTCACCAATACCTATTTTCTTTGTT GAGTGACTATTCCTTTTCCTTTTCAAATTAGTTTGTGTGGCAGTGTGGAAGAACCACCAC ATGAGGACGGTAACCAACTACTTCATAGTCAATCTTTCTCTGGCTGATGTGCTCGTGACC ATCACCTGCCTTCCAGCCACACTGGTCGTGGATATCACTGAGACCTGGTTTTTTTGGACAG TCCCTTTGCAAAGTGATTCCTTATCTACAGGTAATTGTTTTTAATGCTTTTTTGAAGCTA CTAAAAAGAATGTTCAGCCATAGCGATGGCCCTTATGGTAAATTAACTAGTGAGTTGAGA AATATATTTGCCTAAGGCATTGACAAACTGAAGGAAAATAATACTTGAGAATTTCTGGAG AAATAAGTTAAGTTCTGGGTAAAAATTAAGCAATGAACTGCCAAATCATCATTAGATGCT GCACAAACATTTTTGCACAACTTTTTTGATTACTAATTTGATTCCAAAAGTTTGATTTTG CACAAACTTTTTTTTTTTCCAAATTTGATCCCAAAAGTTTGATTTTGCGCAAACTTTTTTG ATTCCTAATTTCCCCATTGTTAAATAAGAAACTTGAACCAATTAATGATTTAACCAATTA ATGATCTCCCCAAACCAATTATTGATCTTTCTCTTGAACCAATTAATGATCTGCCAGTCC AAGTCATTGAGCATATTTGTTTTTACAAGTGATTTTATTTTATACTGAAGAATTAAGACC TACTTGGTCAAATCAGTGCCATGAACAGGTTTTAGTGTAGATTCTAATTCAAACTACCGG ATTTGGAATCTCCGTTCTGCCATTCACCAATTGTATGCTATCAAGCCAAATAGTTGTAAT TCACTTATTTAAAAGAATAATTTAAATGAGATCTACCTCATATGGTTGCTGTGACCATTT ACTTACATAATTCATATAAATAAGTTGGCACAGTGATTACCCTCTGGAAGAGATGATCTT ATAAAAACAGTATATTCTCAATAAACATCAATTATCAGCATCAGAATCATCATTACTAGG TGTTTTTCTTTCCTTAAGAGTGAAAACAGCTTCTTTTTCTATTTAATTGCCATTTCAGTA ATTAAGAATGAATACTTTCAGAGATTAGTGTTCTGATTGTTATTATAGCTCTAAAATTTT TCCCTTAGGAATTGGACAGCAAATGAAATGGTGACCACTCTCTGCTTGTCTTCCCATAGC TTTCCTGCACCCTCAGTTTTTACGCCATGCAGTCTCCCAGATGGTGCCTATAATATTTTA TACTAGACATTATGCCGATTAGGCTTTTGGAATGAAATGTTGCAAAGAGATATTTAGTTC AATAGTTCCTCAATTACCTCTTATAAAAAGAAGTGAAAAATTTTTAAGGTTAAACATTGT TTATAGAATAGTAAGTGGAAAATACTATAGAAGTTATAAGCTCCATGCATATATTATGTT TAATTATAAAGCTAGTTTGGATCAGCCTGCTGAAAATCATGAATGGATTACAAAACGAAC AGTAGCACATTTTTTTGTGTGTGAGGAAAAACTACATGGGACAATAGAGAAAAATATTCT CATAGAGGAAAAGTTAGTAAGAAATGAATGGCTCTGGTGGTGTTTTGCATAGAGGCACTAG GAAAGTAATACATTTCAGATAATTCTAATATTTCATTATCTCTGTGGTACTTCCAGAAAG CCTTTTACCTCTCTGGTTTCAATAACTACCCAGGAGAATATTTTGAGGATTCTCTTAAG CTGTGAAACAGAAGATTCCCTGGTGGGAAGTGAAGTGATAAGGGCAGGTGCAGTCATGTG CTAATGCACAGCGATAGCTTTCTGCAGAGCAGCATCTCAGAGTTTCCTGTGAGTATTTG TATAATCACTTACAGTCCTCTTTCACACAGCAGAACTATTTAACAAGTCCTACAGTTCAA GGAATATCCTCATCTCTGGAAGGATTCTGTCTGCCTCTCTGCACACAGTGTCCAATCTAA TCAATTCCTTAGCTGCTCCTCTTCTCCATAGAGCAAGGGAAAAAACTACTGGGTAACCAC ATGATGCAAAAGACTAGATCCATTTGTTACCCCATCTAACATTACTTCTTGATGGAAAGG TGTAAATGCACCAAGAGATTGGTGCACAGGTAAAACTAGTATCTCCAAATTCTTCATATT TATTGCCTCATTTTTCATAGAATGTTCCCAAATGCAATGAACAGTGCCAATGGGCAATAA ACATATAATTTAAATTTGAGCAGATTTTCTCCCTAGTTGTGACATTCTGTAACTAATGAC TTATATCCCTGATATGATATTTATGTCTTACTGAATATTTAAAAACATGTTACATCATGC CCAGCCACATTTTAAAGTTATTTGGTTGCATTTTAGATTACTTGGACGTTTATTAATTTG ATGCTGTAACGCATTGGCAAATGCACAAAAATCTCAAAAGTCTCACAAATGTTATAAAGC TTAGCTGAATAATTAAAATGACTCTTTTGTATCTTTAATAATTGCATAACTCCAAGACCA TTAACATGTATTCAGCTATTTGCTGAACAATTATCATGTATTTCACTTCTCTCCAACAA

FIG. 1AD

31/51

CAAACAAGCTCCCTCTTTCAGTCATACTTTGAAACCTTTCTACCTATTAGTGCTTATC ATCCAAATCTGTGATTTGGCAAAATTTTCATTTCTCCTTATAGTGAATCTTTAAGATACC TTTGCCGTATCTATTTGCTAGTATAAAACAGTGGACTTCTCTACTAAAGGAAATCCCCAA ACATTATCCTGTGCGAAGGGTGCCCATAGTATAGGTCAAAGACCAAGTACCTGAAGGCAG AAGAAAGTTCCCATTATCTCACTCCACTTCATTCTCAACATTCATAATCCACACTAGATT CATTTCTCAAATGACTTACTATTCAACAAACTTGAGCTAATATCAGAATCCAAATGAAAA AGACACCCAGAAGTGCACTCTTAGAAGTTAAAAGCAACAACAAAACTTTCACTTATAATT ACTTATGATAAAATGCAATTTTACATCACCTCCAAGAAAATCTTATACATTGCACATAAT TGTATATTAATGTGTTAATTGCACAAGCAAATATAGTAGGTCAAACAATGAATATTAGCT CACTGATTGTCAAGGGTTCATTCAATGGATTGGTTCATTCTACTGTTAGATACATCACAC TAGCATATTCCTCCCTTTTCTGTGTGATGAAGGGCAGTGCTCCCTGGGTCACTATTGGCA CTGGATGTCAGTCTTCCAAGTGAACTGATATGAATTGATTATTATGACCTAATGGCATTA GGAAACACTAGAAATGACATTGATATTTGAACCATGCTACATCTATCCCATTTATCCATG TTGATTAAATTAATGGATTATAAATTACTAAGGCTTGATGAACACTTTGTACTTCTAATT GCTAGAGAGGATTGATATATCTCTAGCCCAGAAGCTATGAAAAGGCGACTGTGCGAATCT ATACAACCATAGTTCTATTCCCAGGTTAGCAATGGTATTGAGGGGCCCTAGGTGCTTAAC TTATTTGCAGAGAATGGAGGTTGTAGAGAATAAGGTGATACTGGTTTGAGAAAGAG AGTTGAAGGTACCCTCAGGTAGCACTAAGAAATTTCTAGGAGTCACTAATCAACTTAAGC CCATTCTCATAGAGTCCAGCCCCTTAAAATTACACTTAAAATGAAATTAGCCTCCAATAA TTTAGCAAAGGTTAGGCTTTCACTTGTAATTTCTATGAATATTCTTCTCTGAAAAGCAAT CTGTTCCAATTAAAATATAGAACTTCAGACTCAAGAATGAAAGATAAAACTAATAGTATC ATCATCATTATTATTATTATAATCATAAGAAATAGTAAACACACAGCACTTATATGCCAG CCCTGGAATAGACATTTCATCTCAACTAACTGTCCATACAATTCCATGGTTAGGTACTA TTAATCATCCACATTTTACAGATGAGAAAACTGAGGAATGGAGAGGTTAAATAATCTCCT TAAGATCACTCCATATGTCAGATGGGATTCATGCCCAGAAAACCTGGTTGCAGACTCGAT TCCAGCTATACTCTTCTGCCTCTCCCATAGAGAAACAAAAGAATCATACTTGATAAGAAT AGCTAGCTGATCAGAGAGAGAGACAGATAGTTCATCCTGACAGCCCAGAGACTTTCTGC ACTGTTGCACTGGATCTTAGATCTCTTTCACTCATTTGTACCTATAATCAACATATCAAC AAGAAAGGTCCTCATGTAAAAGACAGAGATAACTACCCTTTCCACATATTATGAGATCAA TATAACCAGGACAGAAAAATAGAAGAAGATGACTGGACTATATCTACTGCCTTCAATTAA GGCTCACCACTATTAATGGATTAACAAATATTTGTTTTAAAGACACATGCAAGTATACGT TCACTGCAGCACTATTCACAATAACAAAAACGTGGAATCAACCTAAATGCCCATCAATGA TAGACTGGATAAAGATAATGTGGTACATATACACCATGGAATACTATGCAACCATAAAAA AGAATGAGATCATGTCCTTTGCAGCAACATGAAAGGTGCTGGAGGCCATTATCCTTAGCA AACAAATGCAGGAACAGAAAAGCAAATACTACATGTTCTCATTTATAAATGGGAGCTAAA TGATGAGAACACATGGACACATAAAGGGGAACAACACGCACTGGGGCCTTTCAGAGGGTA GAGGGTGGGAGAAGGGAGGATCAGGAAAAATAACCAGTGGATACTTGGATTAATACCT CTGCTCATGTACCCCTGAAATTAAAATAGAAGTTAAAAACAAAATATTTCTTAAATGCAT AATGTAAAAGAAATCAGAAGTCTTTTTAAAGGGAGAGGGGATTCTGAGAGTGATATCAGA ATCAATATTTCATCCAGTATAAGAGAGCACATTGAACATAATTACATTAACTAATAATGT GGATATATGAATTTTTAAAATTTTTTTGTTGTTGTTATTTCCTTAAAGTGTCAAGTTAAAG AATGATTTGTGGCATTGTTAATTATATACAAATTTTGACTGGGTGAACTTACCTAGTTTT TGGAATCACATTGACTAGGCTAGCAGTGAGCAAACTGTCATAAGGAGATTCGCATACAAA ATTCTCTTTTAATATGACTCGTAACTTTCCTTGGGTGCTACATGTTGAAAATGCACTGAT GTACAAATAGCCCTTATTATTTGAAAATATGAAATAAGCTACCCATAATTTAAAAATGTT GGGTATGATTTCTTCCAATCAATGGAAAAATTACAGGACAAAATAATTACAGTAATTATT TAAAGAATGCCATATTATAAATTAAGACATTTGGAGTAAAAAAAGATTGCAAAGTTTTCA TCATACCTTTTCATGTTTAACAATAAATTTACATTTAAAAGTATATTTCTAATATTTCAT TTTTGTGATATAATTTCTTTTTAAATAGAAAGCACTTGCATGGATTGTTTATTTTTGGCA

FIG. 1AE

32/51

GCTTTGAATTTGCTTATATGTTGTGACTACCTTTCTCATATAGTAAATATATTAAGAGTA GGTGTCTGTGTCTCTCACACTGAGCTGTATCGCCTTGGATCGGTGGTATGCAATCTG TCACCCTTTGATGTTTAAGAGCACAGCAAAGCGGGCCCGTAACAGCATTGTCATCATCTG GATTGTCTCCTGCATTATAATGATTCCTCAGGCCATCGTCATGGAGTGCAGCACCGTGTT CCCAGGCTTAGCCAATAAAACCACCTCTTTACGGTGTGTGATGAGCGCTGGGGTGGTAA GTACCTTATGGCCCATCAACTGACATTTATATTACAGCAGCAAATTGAAAATTGGATTAG CATAGCCATTGTAAAGCTGGGCTTATATATTTTATTGACATTTGTGAATACAGTTTTGCA AGAGCATGAAAACCAACTTGAATTTCAAAACAATTTCACAGAATAACTCTACCTATCTGA ATCCTTTGGAAATGTTATCTATTATTTTCTCATTTTCATATCTTTTGGATAGGAAATGAA AGGAGATTATTCTACAATTCAGATTTGATTATTTTAGTTTTTCTTAAACTCTTTAAACAA AAAGCAATATGGAATACAAATCCGATTATGTATTCTGGAATGATCCACGATTTATAAGAT GGTTCAACACTGTGTTGTCTAGTGTCAGGGTCCCTAATGGGCTTCAAATACAACTGAATT TTTTCATTTTAAGACCATGTCCTGGATCACATGGTCCTGGGAACATGGCCAGAGTCAGCA TGTGGTTCTCTAAGTCAAATAATCCAAATTTGTTTTCTCTATTCATAATACATTATTGCT ATCTGACAAGTATGATGTGAAATTTAAGCAATCAGGTTTGAAGGCTTTATGTTTCTTTGG TTAGAAATTCTTAGAGTCAGTCTGAGGTTTTTGTGTAACAGTGAGAATACTGCTATCAAC ACCTGGTGCTAGCACAAATCTGGGCACAGGAAAGAATGACAGAAAATAAAATAACCCTGC CCAATCTGACCTCTTCTAGGTAAGTATACTAAAAATGGCTGATATTTAGAGAATTCATAT GTTAACATTGTTTTTTTTAGAAAGATGTATCAAAACAAGCAGTGCACACCAGGGACTGA TTAAGGATAATATTCTTAAATATTGTAATCTTTGAATTTCTGTTATTTCCTACCTTGGTG TTTGTACTAGAACACCGAAAGGAAAAAAAGCCAATCACTGATATATTAGGCATATACTAC AGGATATATCTACAGCAAGATAATATTTAAGAGAGGCTGGGATTATTTCATATATTGTTG CAAGACCTATAATAACTAAAATTTTATAATTTGCTTTATCTATTACCCCAAATATCAAAT TTTTCTCTGTATCATTTTCAGTTTTTTCCAATTTTCCAAATTAATAGTGCAGACAAAAAA AAAATCAATGGAAATTTCCAAAATGGTAGGAATATTTATGAAGTGTCTTATGTCCCATTC ATTTAATGCTCAAACACCACCTTGAGAACTTAGTATATGTCAGGCATTGTGCCCACCTGG AGAGAAACAGACTCTGCTTACGGGAGCACACTCTATATAATAAGGCTCAAAGGCCAATAA ACAAATTTTTATAGGGTAATCAGTATTTTAATATATTATATACAAAATGCTGAGAACAC AAATGAGAGAACAAACTCAGTTCTGGCCATTTGAACAAAAGTTTACAGAGGAACTGCTAA CATTCCAGCAGAACATTAAAGATAAGCAAAAATTCTCCAGACTGAGAAGAGGGGAAAAGGA TGTCCAGAAAGCAAGAAAATCCACATCATGGATACTACATTACAAAGCAGAAAGAGTGAA TCAGCACTTGTAGTTTCTGGAACATAGGGGCAGGTAGTGTAAATAATTGAATTTGAAAC AAGATGGGTTGGGGACTGACTGTGACATGTCTCTTATACGATCCTTTTACACTGGTTTAT ATTTAGAAAGCCTAAAAAGGTCTTTCTCAGAATCCTGTATTAAACTCGAGACTAAATTTA ACCCTAGAAAGATTATATTTTTTTCAAGATTATGAAGCAAATAGGTACATTTAAATCT AAAGCTTCCAACTTGTAAGTTGGGATTCCTTAAGTTTTATAGGGATTGCTATTAGATAAA ATATAAAAATATTTTTCAATATGTGTCAGCAGTATTTTCTCTAATATTCCGGCAATTAGT TTCACTTATATGTTTATGGGTTGCTTTTATAAGCTTTTCTTTTTTAATGTTTCCCTGAA TAATCAAGTAACAGTAACCTCCATTAACAAAAAGATTGCAAAGTCATGGATTCCTGTTCA GTTATTATGATTATGTAAATAGACGTATGATTTTTAAATTACCTCTGAGTGGTAAATATA AATACATAAAGCTCATTTCTACTCTGATATTTTATTACATAACTCTAGCATGGACATTTT CATTAAAAAAAGGAAACAATTGTTGAATATGTAAAAACCTAAACTTAGCCTTCAGAAGTC ATTTAAGAAAACTATTTGAAGGTGATTTTATAATAGCCTATAATTAAATGCTTGTAAAGA CTAAAATTAAGTATTATTGGACTGAATTGATTAGCTACAAAATCCAACTTAGTAAAAGCT ATACAGTCATTTAAATATTAAATGAAATTGCTAAGAATATTTTTAAGAAAAAATAATTCA AGGCAGATTTTTATCTTTCTTATTAGATATTTATTATGATGATTTCTACATAGCATGTAA AATCATTGTTCATGTAAACTATTTATAAGTCCATGTTCGACTTATAATGTTAAACCTTTG TATATGTGTGATTGTCACAACTTTTTAAAAAACCATAGGAAAGTATATTTTACAGTGTCA TCTCTCTAAATTCAAATATTTTTAAAGGCCAACTGTCATTTAGCCTGATTTTTAAAACTA TTGTAAAATATCTTCTATTTGAGATTAATTCATAATCTGTGTTTCTTATCTTTATTCTAA GTTAAATCAATAATGTAGTTATAAAAGTAGAGAGTAGAATCATAATTATCCTACAACCAA AACTTTTGGAAAAGTTCTGTAAATGCTGTTTTACTCATGGTGCAAAATAACTGAGAACTC

FIG. 1AF

33/51

TGTCTAACTAAAAAATTTACCAGCAATATGTAATTATATATGGATAAATGATTTCTAAAA CTAATTATTCATTATTGCCTATTACTTCTTCATAAAAAGAACCATAAGCCATGATTTC TGGCAGACACACACACTCAAGAACATATAAATAATGTAAATACTTATTTTAATAACC TTTAAAATATACATTTGTATGTGTTCACTGTTTGCTTCAGTCACATCATTTCATACTTCT AAAATTATTAAATTAACCCACAATTTCTTGCTTGCTTGGTTTGTAAATGCATAATTCTAC AGGAAAGATCCTACAGAAAGAAATTCTTTGCTGGGTGTGGTGGCTCAAGCCTGTAATCCC AGCACTTTGGGAGGCCGAGATGGGCGGATCATGAGGTCAGGAGTTGGAGACCAGCCTGGC CAACATGGTGAAACCCCGTCTCTACTGAAAACACAAAAATTAGCTGGGCATGGTGGG CGCCTGTAATTCCAGCTACTCGGGAAGCTGAGGCAGGACAATCGCTTGAAACCGAAAGGC GGAGGTTGCAGTGAGCCGAGATCATGGCACTGCACTCCAGCCTGGGCAAAAGAGCAAGAC TTCACTATTCATTCATCCAGTGTTTAATTAGCATGTACCCTTGGTCAATTGTTCTGGACA CTGGAGATTAGTAGCATCTCTTTTTGAATATTACTGACAAATTGTTCTTTGGTAGGCT ${\tt AAAAAAAAAAATGGAACCATTTTTACAGTCAAAGTAATTATGGCATCTGGCCTATTATG}$ AGGTTTGAAAGCATATAAATATGTGTATAAGTCTATTAATGGGAAGATTTATTAAACATA TTTATTAGGGAGAAGATAGTAAAACATATTAAAGATTCAGGTAAACTTAATGAACCCCTA AACTTTGAAAAGACATTCCATGTTGAATATTGGGAAATTATATTTAATTTACTTGTTCAT TCAATTCCTGATAAGTGTACCATGAAAGAGGAATGTTTCTAGTTTCTAGATAATTAAGAT AACATGCTGGCTGAATAATGAACCTTAAGTCATCTGAGAGAAATTAAGTTTTGCCTGTCA AATATACAATATAACTCTTTAATCTCTGATTTCAAAGACTAAAGATCCACATTTGTTCCT TGAGTAAAAACAGTAATTTTTAATGATTATCAATATTTAAAACTTTTTTAAATTAAAGTA ATGCTTATGTGAAACAAATTTTGTGTAGTTATATTCTAGGTTATATACAAATGTCTTAAA TACATTGAAGACATTGCTTATGAAGTACAGAAAGACTTCAAAGATATTTTCATCACACAT AATTTAAAATTTCAATGGCATATCTGAGTTTTTAATCAGCTTAGACTATCATGTTTCCCT AGTTATCTATTATAATCTCCTTATTCAAACAATCTATCCTACCCTGGAAGGATAATTTTG CTTGATCTTTTTCCATATCAGTGTTCATTATAATAATTTGCATTTAGCAGTCAATTACA TATTTTTTCTAATTATTCATAAATATACCAACCACATAGGAGCTTTTGCTACCATCTATT CAAAACGCCAAACTGTTATCACAGTGATGCTATCCATAGCTGCAGTGGAAAAAATTTACC TCTCAAATCTACTTTCCTCTATCCACTCAATTGGTCTTATGCAGACAACAGGGCTTCGCA GGTATGTAAGCTTCAAAGTTATATAGATTTTGTCATGAGGAAAGCTCATGTGACACCTCT TCAAAACAAATAAAAGTTCAAAGCCTCTTAGGTGCCTGGGAAGTGCTGAGATCACTTTCA GATTCCTTTGAAATTGGCCCGCCATATGCTGTGTAGGCTGTGGCACTTCAAAGGGAAAGA CTGTTATTTCTCAAGTCAGAATGCTTGAATGTTATCACTTTTTATGTAACTGGCCTGCTT AGAGAGTAGCTAAAAATGACACCTCAAATTGGTCTCTTAGACCTGCCAACACATGCATCC TACTGACCCTGCTGAAGACTGCAGCGGATAAAGACATCTAAACCAAAAGAGAAGATGGGT TTAGAAGCATGAATATGGAGAAAATTAGACTCAAACTCAACTGCATCTGAAAGACAGCCT ATGGAAATAAGATTGTGGAGGATATTAAACTCATAAATATGTTAAAATATATCCAGCAAG AATCAAATGCATGATTGCTCAATAAATATTATCTATTATTATGACAATCATCATGCTTAT TATTGATTAATCCTGACTGTAAACTGCTCTTATCACAAATCTGATCACATAACCAAGCTT TCATGCTTCTACATCCCCTTTATGAAGTAATGAAAAGAATAAAATACATAGAGGTAATAG CATTATTCCTCAACAATACTATGGGATAAACCCCCTTGTCAATAGAAAAGTCAAAACAAA GTATGTAAATTTTAGAAGAAAAACAAAACAGCTCTGTTGTGTTAGCATTCAATTAGAATT ATAATGAGTTAATTACATTTAATATCTATGGAATCTATGCAAGATATATTGCTTCCTCTT TTACATTGCAGTAAAAGTAGGTAGACCATTGTGATATATTCGAATACAAGTACAAAAATA TCTTCTAAAATCTACAGGGAACTCAAACAAATCAGGAAGAAAAATGCAAACAATCTTAT CAAAAGTTGGCTAAGAACATGAATAGACAATTCTCAAAAGAAGGTATACAAATAGCCAAC AAGCATATGAAAAATGTTCAGTATCACTAAGAATCAGGGAAATGCAAATCAAAACCACA GCCCAGGCTGGAGTGCAGTGATCTCAGCTCTCTGCGACCTCCACCTCCCAAGTTC AAACGATACTCCTGCCTTGGTCTCCCAAAGTACTGGGATTACAGACGTGAGCCTGTAATT GGTGTCTGGCCAATACCACCTTACTCTTACAAGGATGGCCATAATCAAAAAGCCAAAAAA TTAAGGACATTGGAATGAATGTGGTGGAGAGGGAACACTTTTACACTGCTGGTGGGAATG TAAGCTAGTACGACAACTATGGAAAACAGTGTGGAGATTCCTTAAAGAACTAAAAGTAGA TCTACTATTTGATCCATCAATCTCCCTACTCTGGTAGCTACCCAGAGGAAAATAAGCCAT TATACTAAAAAGATACCTGCACATGCATGTTTACAGCAGCACAATTCGCAAATGGAAAAA

FIG. 1AG

34/51

TAGCATAGAATACTACTTAGCCATAAAAAGGAACGAAATAATGGCATTCCCAGCAACCTG GAGGGATTTGGAGACCATTATTCTAAGTGAAGTAATTCAGGAATGGAAAACCAAACAACA TATGTTCTCACTCATAAGTGGGAGGATGCAAAGGCATAAGAATGATAAAATGGACTTCAG GTACTCAGGGGAAAGTGAGGGAGAGGGGTGAAGGATAAAAGACCACAGATTGGGTAAAG TGTACACTGCATGGGTGATAGATGCACCAAAATCTCAGAAATCACCACTGAAGATTCATG TAACCAAACACCAACTGTTTCCCCAAAACCTATCGGAATAAAAAATTAAAAAAATACATA TATGTACTATATAATATATGAATATATCTAATATTAATATACAATATATAAAATTTATAA ATATATAATGATTATATATATATATATATATAAAATATATATATATATGTAGGGAATCTGAAT GAATATATATATATATATATATATCTTCTAGAGCATTTACAAAGTTAGTAATCAATATAA TTTAGAAAAGCTAAAATATTAAACCACAATGCCATGAAGTGATTAATCGACTTATTCGTA ACTACAGTCCTAGAGGTGTTTATGCTTAATAAGTGAGAAAATATTCATATTGGATTGGAG AAAATAAATGTTATAAAGCCTTAAAATTCTCATTTTTATTAAAAGTATATACATGTATTT TTAATAAAGCATACACACCACAGACATACTATGCTTAAAGAGGAATTTTGTATATGT TCCAATAAGTCAACAAAATAATCATTGTCAAATTTGTATTGTATTTAGTTTTCAAAATT TTTTTCACATTTGTATTTGGAGATACAACTGAGAATAGCCTCCCATTTCTCAGGGAACTT ACATTCTAATAAGGAACAACCAACTGAGTTTATATTTTCTTCCCATTTTAACCAAAGCAT AAATTAATTTTGTTAATTAGCCAGATGTAATCAAGTCAAATAAAGGGCCTTTTAATAACT GAACACTTGACTTTGGGTAGCACAAATTAAGAAATAGCTAATGCTTATTTTTCTGAGTAC ATTAAGTGAAATTACGACTTCACATTTGGCATGTGTATACCCATATACTGAGTAAAATAA ATAAAAGGTAAATATGCACTTTGAAGAAAAGCATTGACATGTATCTTTTTAAAAGTCCA TCAATTGTAACGTAAGGTTTTGTTGTTTTTGACTTTCATCCTAGGTGAAATTTATCCCAAG ATGTACCACATCTGTTTCTTCTGGTGACATACATGGCACCACTGTGTCTCATGGTGTTG GCTTATCTGCAAATATTTCGCAAACTCTGGTGTCGACAGGTATATAGTTTCAAATATTTT GTGCTTTTTTTTTAGGATGCACTTATAAACAAAATTTAAGAATGCATTGAACCAATATAA CATGTTCATAAAAGTATTATATTGTGTGTTCTTTTAAAGTAATGAGAACCCAGACATAGA AATATGTCTAGGCATTTTTAGAGTAATATTCAGGAAATGTATTTTATAAACTGATTAAGT ACTTTACATTTTAAATAAAATTTAACATCTGTGATTAATTGTCTTTTGTCTAGGAATAAC ACTAATTTCGCTTTCTATGAGAAATAGCAAATAAAAATTCCTTTAGAGATTTTTGAGACT CTAAGTCTGAAAGGTTATATTTGTAATCAGATTTATTTAAAACATTGGAACATATAGGTT AAATCTCCAACTTCAAAGATCTTATTTTTTAGAATATTATAAGAATCAGGCAGAATGTAT AATTTTAAAAACTGTATATAATGCTGATTTGGGGTTACTACACTTTGTTAGATAATTCTG GAACTTTTCACATACATGTCTCACACAAAAGCTAAAAATTCTACTTTTTGCCATTGAGGA ATTCATAGTCTAGAGGGGGGCATCATCAGATGCAGGGCGAAAATTACTTTAAATATAAG CACAGAGAATCAGAGCAAAATGTACTAAAACCATATCTAATACAGGAAAGGTAACATTTA AGAGACAAAAAGGATATGGCTCAGTCTCTCCCATTTTGTAAAATGTATCTTAAAATGCCA GGCTTGTGGAAGGACATGCCATTAGTCTGTTTTCTCTGACACATTTTATCCAACTGAAAA GATTTACTGGAGTCACCTTAATTCATTAAAAAGATTTCACAAACACTTTATTTGGTCTTT GAGGATGTGTCTTTGTTTTTTAATCAACACTTGTTATTCAAAGCATTTTTCAAGATCAT CTTTCACTGACTGGATATGAGCAACACTCATTTTTTTTAACACTATATGGCTCATAATTT CAATATTTTCTCTTTTCCTCTGCTATTACAAAGAAGTCATTTCTTTTATGACCTTACAAG TGAAACCAGTAGCAACATTTATTAACATTTTGTTTCCCATCATTTTTTACTATAAAAACT AATGTGGACCACTATAAAATATGAGTGGTGATTTTCTAGATGTTGGTGACAGTTTTCTCA GCACTCTCCACCTCCCTATGAAGCCAATGCTTATATTTTAGGGTGTTTTGTTACTGCAGCA

FIG. 1AH

35/51

TCCTGCTTCCTAGTACCTATTATTGTATCTGTCAGGTTTTTGCTAGGTTATTATTCTTCTA TTAAAAAATGTGGTTTGCAACAACAGTTCTGTTTCACTCCTATTACAGGTCAGTGGGGAG GGCTGGCTGGGGCACTGTGCTCCATTTGTTTTCTCATTCCAGAACCTAGTCTGAAGAAAT GGCACTTTCTGGGACATGCCATTCTGAGACTGAGAGAAAAGAAAACTGGAAGAAAAGTA TATTTTCTTTAATGTCTTTTATGAACCGGCATGTGTTACATCTCACTTTTCATTGGCTA AAACAAGTCACGTGGTTAAACTTGATCATGAAGAGGGGACACATTCTTCTCTGACAGAAA ATGATACACTATACAGAAGTCAAAAACACAAGGGCCAGACTGCATGAATTTAAATCCTGA CTCCACCAAGTAGTAGTGACATGAATTTTGTAAATGGCTTAAATTTTTGTGACTCCCTTT ATTAACTTTAAAATGGGGTTGTATAGCATCTTCCTCATAGGTTTGGTACATGCATTCAGG TGTGTCCAAGGGAGAACACCGTCGTGGGTTCTCAGTTTCTATTTCTATTTGGGCCAGT AAAACCCCTTCCTATCCCTCTTTTCTGCTTATTACTAGAGACAGAAACTAAAAACCAGGG CTTCAGGCTGCTAAAAGCCTAAAACAAAACAAAACTACAACAACAACAAAATAAGGTG GGTTGGACAAGCTTGCTTAGATGAATTAACTCAAGTGCCTAAATATAGACAGTGCTCATT AAACAAAATATCTTAATGGATGTTGTTTAATAATGGCCTCTCAACTAATTGTACTTACAT TTAAATAGCAAGCATGTGTTGAATTGGTATATGTGACTATTTTTTAAAAAATGCACATTG AAATACCAGTATGGTGCTTCTTATTTGTCTGGTTCTTCTACTCTACTAAGATAAAGATAG TCTCGCTGTCATCTTTGTATCCCTATAAATAGCACGTGCTCAGCACACATCAGTTGCTTT TTTCATAAGAACAAAGTGAGTAGAATAGGAGAAAGTGCTGGGAAAGTTTAGAGAGGACAT AGAGAATCTATTGCCCAGTTACTCCGATAAACATTTGTAGAAATGGATTAGAATCTGAAA AATTTCTTGAAGGGGAAAAAGCAATTAATGAGCATGTAGGAATAAAGATATTTTAGATTT AGATTCAGATTTTGTTGGGGAATGTTCAGTGTTAAGATTATCCCCTATTTCCTTATTTTT ATTGACATACCTTTAAAACTCTTTCAAGGTTGCAATGTATCTGTCTTGTTACTTTTACAT GGTAAAACTTTACCATGATACCATGGTTACCCTAAAGTTTACATGGTACCATCAGAGAAA ATGTTTTAAAAAGTTTGTTAAATGAATGAGTGACACCAAAATCCAAACATTTTAATTTTC GCATCACAGATTCATAAATAATCCACATTCTTTTCATGAATTATCCTCATTAGTACAAGC CACATGATTCAGAAGATTTGCAGTAAAATGCTTGGGCTGTGAAACTAAAGTCATTTACAA AACAGATTGGAATGGAAAATACCAAGTTCAGCTGAACTCACTTTAGCAGCCACAATAAAG TGAATTAACCCCAAATGCGTGATTACATAGAATTCTGCTTGAGCAACTCTCAATTTCCAA CTGTTAGTGTCTATAAACAAAGTTGTAAGGCATTATGCGTGCCATAGGCTACATCAAGTG AGCCATCAAATGAAGAGCTTGTCCTATTTGCTTAAAATTACAGAGATGCATGAAATCTGT TATGTACTTTTGAATTAGTAAGTGTAAGATTATTAGTGAGCAAATTGTGTGTCCTTGTCT GACTTTCTCAAGAAGTTTAAGCCTCATTAAAAGAATTAGCTAATGCATTGCTGTGAACTA TCTTTCATTTATCTGTCAGCATTTTTTCTAGTTCAGACCCTTCATATAATTCAACACTAA ATCTTAATCGTCATGTGCTTGTGTTAATTTATTTCACATTTATTAAGCACGTACTCTGTG TCAGCTATGGTGTGAGGTACTGAGGATGGACTGTAATAGATATTTGGGTCTGAAACTATA GTTCAGCTTCTCAGGGCCTTTGAAAGACCTTCTTGTTCCCAGCTCTTATCACAAAGTTTT ACAAATCAGTCTAGTGTGAGAAAATAGGCAGCAAACAAATTACAATTGCAGGGGCAGAAT CAGGAAGGCAGTAACTCGAGTCCATACAAAAAAAAATAAGGAGCACCAGTAAAGGTAACT ACATAGGTAAATACTGTAGACAGAATAAACATATTTATCTTCTGTTATCTGATGTAAAGA ACAACTGCATAAAATAATAGCTATAAAATTGTGAAGATTCACCTTATAATGTATACAGAT GTAGTTCAAAAAGGAGGAGGAAATGGAGCTGTATTGGAGCAAATTTGTTTTATACTATT GAAATTACATTGGCATAATCTAAGCAGCTTGTTTAGATTAAGTTGCTAATTTTAATTCCT GGTGTAACCACTAAGAAAATAATTTTTTGAAGAATGTAGAAATATAGGTAAAGTAACAAA AGAATTAAAATAGTATACAGAAAATATTTAACACAAAATAAAGCAGTAGTGAGGAAATAG CTGTCTACAAGAGACATACCTTGTATTCAGATATACAAATAGGTTAAATGTAAAATAACA GAAGAAGTACTAAAATAATCACAAAAAGGGAGTTAATGTGGTTATACTAAAATTAGACAA AATAAATTTTAACAAAATATTACTATACATAGAGAGGGACATTTCATAATGATGATGAG TTGATCCATCAGGAAGATATAAAAGTTGTAAACATACATGCATTTAGCCACTGAAACCCA

FIG. 1AI

36/51

AAATATACCAAGCAAAAAGTAGTAGAATTAAGGAGACAAGTAGGCAGCTAGACAATTATA CTCACCCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGTGGATCACGAGGTCAGAAG ATTGAGACCATCCTAGCTAACATGGTGAAACCTCGTCTCTACTAAAGATACAAAAAATTA GCCGGGTGAGGTGGGGGCACCTGTAGTCCTAGCTGCTCAGGAGGCTGAGGCAGGAGAAT GGCGTGAACCCGGGGGGTGGAGCCTGCAGTGAACAGAGATCGTGCCACTGCACTCCAGCC GCAGAATAGCAACAAGGAAATAAAAGATTTAAACAAACTATGAAACCACTGGGCTTAACA GATATTTTAGAACACTCCACCAAAAACAGAAGAATGCATATTTATCCCATTTGCACATAA AACATTTTCCAGGTTTTCTGACTAAAGTCAGAAACAAGACAAGTATGTCTGCTACAACCA TTTTCATTCAATGTTGAACAGAACTGATTCTTTTCAGGGCAAACAGGCAAGAGATAATAT TAACAATAATAAAAAATAAAAGGCATGACGATCACAAAATAAGAGGTAAACTATTTCTAC TTGTAGGTTATGTGATATTTTATATAGAAAATCCTAACGAATTATTTTGCAAAAAAATAC AATCAATTTCATTTTTATACATTAGCAAATAAAAATTTAAAATGAAATTAACAAAAAATA ATTTAAATAGCATCAAAATTAATCAAATACCTAGAAGTAGATTTAATAAAAGAAGCTTAA TAAGAGACTTCATCCAGGCTTGATTGCTTATGCCTGTAATCTCAACACTTTTGGGAGACT GAGGCGGGAGGATCACATGAGGCCAGGAGATCAAGACCAGCATAGTCAACGTGGTGAAAC CATGTTTCTACTAAAAACACAAAAATGAGCCAGGCATGGTGGTGCAGTGCAAGACTATAA TCCCAGCTACTCAGGAAGCTGAGGCATGAGAATCATTTGAGCCTCAGAGGTGGAGGCTGC AGTGAGCTAAGACTGCACCACTCCAGCCTGTGTGGCAGAGTTAGACTCTTGTCAA AACAAAAAAATTCTTCAGCATAAACATGTATATTTAGGGAATGTCCAGAAATTATAGAG ACATGGATTCCATGCAGCAGTTATAATTCCCTAAAAAGAGAAATTATGAATTCACTGTATT GCTGAGGATTCTAACATAACCACCAAAGATCCAGGGAGAAAATTACCCTATTTTTGTATT TAAAAAGATGCATTTATTAAATGATGTGGTACTAGTCTCTATATAGGCAACAAAAATAAT GAAAAGGAAATAGCTCTGGATTATTAAAAATAAATAGTCTGTTAATCAAATCAATTAAAT AGATAATGTTCCTTCAACATTTTCAAGTCCTATACATGAATATCATTTACAATCATAATT ATTAGCAACTTCAATGAGTAGGCCACAGTTATACAAGTTTCTTGAGTCAGTTTGGAACTA TTTCCATTCAAGCAACATATAGTCCATTTCTGTAACATTTTGTTCTCCATCATTATATTC AGTCTCAGAAAGGTTACCAACACAGTCCTTGAATCACATGTAGTACAGGTTAAGCATCTC TAATCCCAAAACCTAAAATTCTAGCTGCTCTAAAATCCCAAACTTTTGAGAGCTAACATG ATGCCAGAAGTGGAAAAGTCCCCTGCTATCTCATGTGACAGGTCGTGTCAAAAGTCAACA AAAACTTTGTTTCATGCCCAAAATTATTAAAAATGTTATATAAATTTTGTTTAAAGACTAT TTGTATTGGGTGTTTATAAAATGTAAGTAAGTTTTGGGTTTAGACTTAAGTCACATCTAC AAGATATCTTTTTATGTATATGAAAATAATCCAAAAATCCAAAAAAACTCACATCTGAAAC ACTTTTGGTCTCAAGAATTTCAGATAAGGGATATTCAATCGGTACACAACATATACACCT ACAATTACAAAATATCATTGAAAAAACTTAAAGAAGGACTACCTAAATTAAAAGATATTC TGTGTTTATGGATTGGAAGATTCAATCTTGTTAAAATAGAAATAATCTTCAAATTAATCC ATGAATTCAATACAATTCCTATGAAAATCCCAGATGGCTTTGTATTTTGGACACAAATTG TGAAAAAGAAATGGAAAACTTACTTCCTAATGTCAAATCTTAACAAAAAGCCACAGTAAC TAAGACGGTGTGGTACTTCCATACAGTTAGTCATATAGATCAGTGGAATAGAATTCATGG TCCAGAAATAAACTCATATTTATGATTAATTGAGTATTGATAAAGGTTTTAACACAGTTC AATGGCAAAAATCATAGTCCTGACAACAATGGTGTTAAGACAATTGTATATCCACAAGC AAAAGGATGGAGTTGAACCTCACCTCACACCACATTCAAAACTTAACTCAAAATGAATCA TAGATTTATATGTAAGAGCTAATCTCTTAGAAGAAAACACAGAAGAAAATCATCATGACC TTGGCTTAACCAATAGGTTCTAAATATAACACCAAAAACCAAAAGCAACAAATGACAATGT AGATACATTAGACATTATCAAAACAAAAACTTTTGTGCTTCAAACTGCACCATTAAAAAC GTTAAAAGTCAGCCCATATAAATGCAGAAAATATTTGCAAATCATATATGTGTTAAGGAA TTTGTATCCAGAATATACAAAGAACTCTTATGAATTAATAATTTAAAAAAATTACAAGTA GGCAAAGACTTGAATAAACAATTCTGCAAAGAAGATATACAAATGGTCAATAAGCACATA AGAAGGTGCTTAACATCATTACTCATTAGAGAAATATTAATCAAAATCATGAGATACCTA TTCACACTCAACAGGATAGATTTGTTTTAAAAGGCTGTAATCATTATTGGTAAGGATGTG GAGTAATTGGAATCCTTCTACATTGTTGGTGGGAATGCAAAACGATGTAACTGCTTTGGA AAACAGTTTGGTAGTTCCTTAAAATCTTAGAGAATTACCACATTACCCACTAATTCAATC TCTAGTTATAGACCCAGAGAACTGAAGACATGTTTACACAAAAACTTACACATGAATGTT CATAACAGCATATAATTCATAGTAGCCAAAAAGTGGAAACAACCCAAATGTTATCAATGA

FIG. 1AJ

37/51

GTAAATGGAATAACTCATTGTTCTATATGCAAGCAATAAAATATTATTCAGCTACTAAAA GAAATGAAGCACTGATATATGCCACAAGATTGATGAATCTTGAAAACATACTAAGTGAAA GAAGCCAGGCACAGAAGGCCACATATTACATAATTCTATTTGCATGAAAATGTTGAGAAT AGGCAAATATATAGAGCCAAAATAATTTGTCCTTGGCACGGGCTGGCAGAATGGGACAAT GAGAAGTGACTGCTAATGGATTTGGAGCCTCATTTGGAGGTGATGAAAATGTTCTAGATT AGTTAGTGATGATGTTGCACAACTCTGTGAATATTCTAAAAATCATTTTTTGAA CCCCTTAAAGCAGTGAGGTTTATGGTATGTGAATTATATCGCAATAAAATGTTTTCTTTT AAAAAGAAAGAACAAAAATGATGGGATATTTTAAAAATTTTAAAAATTGAAGACTTTTTTT TTTTTTAGAAAGTTCTGCTGCTGAAACCACAGGGAAGCAAAAAAGGTTGAACACACAATT TGACATGTTAATGTAATGAGAGACTATAATAGGAATTATCCACGGGTTGTTTTATCTGTA CTTTCTGACTAAAGTTTTTTCCGTACTTCTATAGACTTTAAAATGGTCCATAGATGTGC AAAAAATGAGAGAACCTATTCCATGAAACCATATATCAAGTCCCAGAGAGCAGAGGGAAA ACCTTTTTTTTTTTTTTTTTGCAAAGAAGAAGTCATAGACTGTGTGAAAGAATAATGT TGCGAGACAACAGATCTGGAGTTGGACAGGGGCAGGAGGCATAGTGAGAAGATCAGTTAT TGCAGTTGTCATCCATAAGGGCCATCTGTACACTCTGAAAGTGGAGCTATTCATAGTGAG AATGATGTTAAGAAAAGGAACAAATAAAATTACAGTCCTCGTTATAAGAATTTAGCATGC AAATCTTATCAGAGCAGTACTGAGGTAAACAAAAGTGTCAAGAAATCATGGGATTTAAT CAAGGAAAATTTTCATGGTCCCTGCTGAACAGGGAAATGTAAGGGGATTATTGTTTCATA GAAGACCGCCAGTGCCTACCAAATATCTGTTATACTCTATTATGATGAAATGGGTAATAG GTTAAGGAATACCATAAGGGGAAAGGAGACTTGTCCTACAAGTTTCTTAGCACTTAGCAA ATGGAGCAGGCATTTGCTATGCATTAAAAAATAAGCATCATCCAAACTCTCAGACTCATC CAGCCACAAACTTAACTTTTTGTTCCTCCTCCTCCCAGATAAAATTCTCGACTTATTTCC ATTTGTCATCTTTTTCTCACTAACCGCCACCTCCACTGATGTCTCAGCCCACTTCAGTGT AGCTTCAGCTTTCATCATTACAGTGAAACAGCTTACATGAAAGTTACCAATGATTTCTAA AGAATATATTTTTAAAGTTTATTTATTGATCTTTTTGGCAGCATTAAGCAATGTTGTTT GTGGTTTCATTGCTCATATACTTTCTTCCTACTTTGATTTGAATACTTTTTTGCTTTGAAT ACTTACCTTTCCCTGACCAGTAAATGCCACTTTGCTAGGTCTCTTCACAGCTCCAT GCTTTTTTCAGGTAGTCCCTTGCCCAGGTACTTTTTAAGTGAGGTGAGTATCAAATATA TATACACATCAGACTAGTCCTCTGGGATACACACAATCACAAATACACTTAAACACTCAA TGTACCTTTATTATAAATCTTGAAATGAGTTTTTATAAGTCTTGCAACCAAAGTTTAAAA AAGAATAAATTCTTTTTTTAAATTGCTTTTGGCTATTCCAGGTCTTTTGCACTTTCATAAA AAATTAAAATTAGTACTTTCATTTCCAGAAAAAAGACTGTCGTGGTATTGAACGTGATTA ATTGCATTAACTCTATAGATCAATTTGGGGAGAATTGCCATATTAACAATACTAAGCCTT TTAATGCATGTCCACAATGAATATTTTATTTAGGAGTTCTTTATTATCTCTCTGCAATG TATGAAATATATATATATATATATTTTATGAAATATATATATATATATATATATTT TATGAAATGTATGCCTAAAACACATTCTTTTGATATTGAAACTTTTAAAATTTAATTTTC CTCCTTGCTAAATTCTTTTATAAGTTCTAGTGGGTTTTTTGGTAGATTCTTTAGGATGATC TTTCTTCTTGTATTGGCTCAAAGTCCAGTACAATGTTGAGTACGAGTGGTGAGAGAAGAC TTGATTTTTGAGTGGTAAGCCAACACTGCATTGCTAGAATAAATCTGATTGAGCAAATG GTATTATCCTATTTATATATTGCAGGATTTAATTTGATAACATATTTTTAAAGAGATTTT TATCTCTATTCATGAAGGATATTTAGTTGTTAGCTGTCTTTTGTTGCCATATCTTTGATT ACAAAGATAAATGTGACCTCATGAAATTTGTTGGAACATATTATATTTTCTGTACATTTC TGGACCTATCTGGGCCTGGAGATTTTCTTGTAGCATAGTTTGTAAGTACAGAGTCAGTTT TGGTCATCTTTGTCTCTCAAGGGCTTTGTCCATTTCATGTAAGTTGGCAAATTCATTGTT TATCCATAATGTTTTAATGTTTGTAGCATGTTTGCCTCTTCCTCATAACTTTATCCTGG TCACAAACATTTTTTAAGACAGAGTAGGTTTTAAGGTCCATCATGTACATGCTATTTCCA ATTCATAACTGTGGTAATACATTTTTCAGGGTGTATTTTTGCATTAAATATGATTTATAA AGTTTATTCATAATAGTGAAATAAAAGTGGGGTGCATGTATTTTACTTAATCCTTCTCAG TGCCTGCTTGATTGAAACCTCTGAGATTTACAATAATGTACTTTTAGGGATGCATTAAGG ATTACTAGTGCATAGTTCCTGGAGCTCAGTAATGTCAGTTATTCCTCTTAATTTTATACG GAGTTTCTCTGAATTCTCCATGTCTCTAGACAGCTTATCAATGGAGAAATTTATGTGTCC

FIG. 1AK

38/51

TCAAAATGAATGCAGGATTCAGCATCTTCTATCCTTATTTAGATCATTATCTAAAAAGGG CATCACTACATTTTTTTTCCCGATTTCAGGGACCATAGCTTTCTCTTTATGAAAACTGT ATTTTTTTTTTTTTTTGAGATGGAGTTTTGCTCTTGTTGCCCAGGCTGGAGTGTAATT GTGTGATCTCATCGGCTCATTGCAACATCCACCTCCTGGGTTCAAGCGATTCTCCTGCCT CAGCCTCCTGAGTAGCTGGGATTACAGGCATGTGCCACCACGCCCAGCTAATTTTGTATT TTTAGTAGAGGCGGGGTTTCTTCATGTTGGTCAGGCTGGTCATGAACTCCCAACCTCAGG TGACCGAAAACTGTTTCTAATGGCGGCAGAAGTCATCAGATGCAGAATGTAGATTCTCTC CTTCAGGGGAACAGTCAGTGATAGAATCACTAAAATTTAATTGATCTATCAGAGATCATT TAGAAGACAGACAGTTCAAGATCATTTAGCAGACACATACAGGCTTTTCATGATAGGAGT CTCCTGGAACATTCCAGCATCCATTGCTCATTCTTTTCAGTTATTTTTTAAAATTGCTTT TTAAAATGAGAGTCACAGAAGAGAAAGTTCCTATCTCTCCCCAACCAGTGGGTTAAAAGA TTGAGTTGAACCACTACTATGTAAAAAAGATTGTCTACATGACAAGACATACAGAGTGAG AAGAAAATAATTTATCCGATATTTTCCATTCAAGGGCAGGTCTTTGTTAACATCATTTG CCTCTTCAAGAAAAAATGGTCAAAGGAAATGTCATATTAATTTATCTGTGTGGACATA TAAGTAAAATTCTGTTCTCAAATTAAAGATTATCGAACAGACTTTGATCTGGTGGTGTAA AAATCAACAAAATCTATCGAACATCTATTCTGAGAAACCACAAGGACACATTGGTCAGTA CTGGTTTGCCGCACAGAGACAGAAAGTAAAAGCTGAATAATCTTAACAGAGCTAAGGTGG TTGTTCTGTTCACTAAACCCTATCAATCTTCATGAGCTTACAATTAAGAGAATATTGTAC TTGGAGGGATTCCCTGCTATTATCAAATAACTTTGAAAAGAAATGGAAAAGTACAAGTTG TGTAATTACTGTTACAAATTCCAGCTATTTGAAATATTAATGTAAGACCGCAAAAAATCC TCAATGGGTTTGTGTGCATTTTAAAGGGCTGGACCACAAAACTGATTTCAAACAATTTCA AGGTTTGCTTTGTCCGAACTCGAGAAGCAGAAAACCTGAAAAGCTACAGGTAGTTAAGTT CTATCTCTGGCAGCAGATGGCAGTATTGATGCGTGAAAAATCCATAACAGGTTGCTTG ACGTTACTTGCTGGGTTTTCCTCTGCTTTAAACTTTGGTATCTGAGCTGAACAAAAATTC CTAATAAGATAATATGGCTGACATCCCTTTATCATTCTCCTTTCCCAAGCTTTGTTCTTT TTACAAGGAAATATCTTTTCCACTTGCAGCTTTCTTTAGACATTGACAAAATTTTGATGT TTTAACTTTTTTTCCACACAAACTCCTATTTGGTATTCGTCTGAATTAACGCCAAGCAC ATACTAAGGTCAGCAAATGCTCTGGAGAAACAGGCGCTCAAACCTCCCACACCTCAGGCG TCTGGAAGCCTTTCCTTACTGTGTTTTCTAATTACTTCCCCAAAGTGGAACTTTCCTAAG ${\tt TCAAATTGCAATAAGGGTCTGTCTCTTCTCCTTTCAGATCCCTGGAACATCATCTGTAGT$ TCAGAGAAAATGGAAGCCCCTGCAGCCTGTTTCACAGCCTCGAGGGCCAGGACAGCCAAC GAAGTCCCGGATGAGCGCTGTGGCGGCTGAAATAAAGCAGATCCGAGCCAGAAGGAAAAAC AGCCCGGATGTTGATGGTTGTGCTTTTGGTATTTGCAATTTGCTATCTACCAATTAGCAT TCTTGATTCTTAATTAACTTTTTTTTTTTTTTTTTTAACTAAGCCAGAGAAAAATCTAAACT TTCTGCTTAGATACCTTGTCAGGCCAGATGACTCAGTTATGTTGTTACCAGCAGGTAAGG CGAACAGCCTTTAAGAGTGCTCAGACATGTGCTTTTGTCATGCGTATTCTCAGTTGCATG GCAGACATAAAACAGATGTTTCTCCAATCTCTTCAAGCTAGTTGCTAAACCTTAGATGCA AACGGGTTTTTCAAAACTTCGTTTCCAAAAACATAGGCAATTGTGAGAGAATTATATCTT AAGGATAAAAAGAGATAAGAACCTTATGTTAGTATTCTAATTATACTTAAAAGTGCATTG GAATTCATTTCCTGAAGTCACTGAATGAAGCTCAGGGCAGATAGTAATAAAAATCAATGA GGGAAAGTATGCTATTTGCTACAATGCAGGCACAACTATTAAGTTAAAAATTTTTGACCCA TATTGGGAATTATCGAAACTGTTCCACATAGACTGGTCCCAAGGCAATACCAATTCTTGT TTACAACAGGCTTCGAACTTAAGCTAGAATTGCTCCTCTCACTTTGGCCTGATTCAGAAT CAATATTATATTCCTCACAGCTGGGAACTCTGAAGAACAGCAGCTTTGGCTGGAGTCAGA AGAAGTGGTATAATCAGCCGCAAAGGGTTCTCATTCTCTTTTGGCCCCTGTTTTTTGATGGT TTAACGGCTTTTTCAATGGAGAAGAAATGGAGAACAAACTTCTGTTCAGTGATACTATTT TGCCAGCTCACAAGAAAATAGAAATTATTTTGCCCTCCATATCTTTTTTGTGCTTTC TATTATGGCCACCTGCTAGATACTCTCTTCTGCTTTTAAGAACTTTATAAACATGTTATG

FIG. 1AL

39/51

TAAATTCAATGAAAATTGGATTTACCTCTCTCTGGGTTACGTATTTGGATTTCCTGTATC TTCTTCTGACTCAAATCCCTTCCTTTCCAAGGAAAACAAATAACTTTCAAAGGAGCAAGG CTGTGTTAAATTTAAGATATTTCAAGTTTTGGGGCATTCTACTCTTTTCCACAACATAAA CATTCCTAGCTTTTTCTCCTTAAAACTTAACTTTTTGCCAAATTAGTCAAAAGCAATTTC TTTACAACAGTTCAGGTTTGTCCAAGATTTCAAAGACATTTTGAGGTAAAGGGTCATAAC ATAGTACAAATTTCTTTTGTCCGTATTATTTCACTCTATATAGTATTTTTGTAAAACTCT AGTACTCTTTATACCAGAAATGGTATAAGGTACACCTTATACCAGAAATGCATTGTTGTC ATCTTATTGAGTAGCTGTAAGTTATCTGTTATAGGTTAGTGATTAGAATTTATAGATGGA ATATTTCTAAGTATGGAGAAAATTTTTTAATAGTCTTTAAGGATAGCATAACAAAACATT TTTTAAAGTTTAAAATAATACATGAAAAATTAACACTCATTAATTTTTAAAAATTACCAA AATTCTGCCCATCGAGAACTGTTTCTTCTCTGGGTATTAAGGAGTCCCAGAAGGCAAGTT TCAGATAGTCCAGGAAGATTGGAGTTGAAGGCATATGATACTTTGATCAATACATAAATG AAAGTAGGAAGAAGTACTTGAAGACTATCATTTAGGAGTGATTTTTAAATGATACACATA ATATATTCAACTTCCATATTCTTATTTACAAGAAATACTGCATCTGCTATTTGTGGGAGG GTTCAGGCACTGAAGTTATTCTAAACCAATTATGGGGTCAGAAACCAATCTGTGGTCAAT TCCTGCAACTGAAGAGGACAGGAGTCAGACCATCCTCTACCAATAGCCTTGTTCACCTTT GAATTTAATTATTAAAAGACACTTTTCTGTTGTTTCTTTTCCTGCAGAGTATTTGGGAT GTTTGCCCATACTGAAGACAGAGAGACTGTGTATGCCTGGTTTACCTTTTCACACTGGCT TGTATATGCCAATAGTGCTGCGAATCCAATTATTATAATTTTCTCAGTGGTGAGTTTTC AACTGTTCTTCCATAAGCCACAATTGTAACCAAGGATGAGGAATCAATGAACACTCTTCA ACTATATGAGGAGTTTAGTTGCTATGTGAGTTGTATTTTTTCCCTGACCTGATTTATCTT GAGTTTCTTCTCTTTTGAGGCAAAGTATTTGTTACTGAACTCATCAGAGAAAATGAACTG ATTTTTCCATGTCAAACGTATAAGAAATGTTATAATAGAAGAAAAGTAAACATTCTGAGA AATCAATAACACAAAATCTTACATGACATACTTTAAACTCATGATTTACAAAAATATAAA ATACTTTGTTCTGTTTTGCCTTGCTATATTATTCCTTTGCCAAAATGTGTAGCCTAATTG AGACAGAATTGGGATCTATTCACTTTTAGATATTTTACTATATTTACGTTTCTCTTGTGA GTATCATCTTGGATTTATCTCAATATTTCCCACTGACTACCAAAAATAGTATTACTCC AAAATAACACATAAGTTAAATGATACACACATACATATACGTGTAACTTATACAATTTGT ATCTGTTTATGGAATCAATATAATTATAAAAGTCATTTAAATCACTATTGTTTATTCACA TTTTGCCCGACTGACTTTTAGAATTATTTTTAATTAGCTACCTTTTTTACATTGCCTTAAT CTCCAACTCATTGGCGATTTCTTTGTTATTTCTATCTTCAAATATATGGTGATTTTATGT GGAAGAATAGAAATTCATTTTGTGGCATATTTAATAAAGCTTCTGCATCTTCCAACTTGA TCTTTGGCCTTCTGGTTTGCATAGGTTTAAAAAAAAGGCAACAAATTAGATTGATGAGAA ATAATTTTGTTCTATTTAAAAAAAATCTAGCACAATGACTAAAGCTCTGAACCTCGCAC TAAGCAGGTAAAGGCTATGAGGAAGTTGTAATGAGAAGTGTTTGAAGCAGAAGTCACAGA ACCAGGTCAAAGTCCTAGTATGGAGGATAAAAGTGAGTTAGAGGAGGCAACTGATAATCA $\tt CTGATAACTCATTATGTGACTGCTATTGTGCTGGGCCCGTGAACATTCATCTTCTCATTT$ CCATTCACCACTAATAAAAGTGATTCATTCATTCTCATAGTTCTCCAATATCTCCTCCATA ATTTAAAGACAAGGAATAGCTTCTACAGTATTTTTCCCCCTTCAGTTTTTTGTTCTT ATATAGATTATGAAAACTGAAAATTTTCTGGATATTTTGAGTGTATGTTTCTAGGTATTTTTG TGGATTTAATTGTTTCAGTATCAGTTATTTAGAGTAAAATGCAGGAGTAATTTTTGTATA ATTTTGGCTTTGTATGACATAAGTTTCATTGTGTTTAATTATTAAATATCTCTGAGAGTT CTTCTACTGATGATCACTTCCATTATAGTTATGTAGATAAAATATACCAATATGCGTAAA TATATGAGGTTTGACTATAAAGGAATGAAGCCAAATTCCAAGCCCCATATGTGAAAGGCAG CCTCGTTATTTTATGAAAATATTCATTGTTTCAAGAGTCTACCAAGCTTCCAATAAACTC AATTTCCTTATTCTATTTTACCCATCTTTGCAAAATATTACACCTCATTGTTAGTTTGGC TCAAGGGAGCAACTCAGTTGTACCCTATTCATAATTTGTTGAAGCATTTATGTATAATTC CTTTTCCTTTCATTCTCTCTGTTTGCCAGGAAAATTTCGAGAGGAATTTAAAGCTGCGTT TTCTTGCTGTTGCCTTGGAGTTCACCATCGCCAGGAGGATCGGCTCACCAGGGGACGAAC

FIG. 1AM

40/51

TAGCACAGAGAGCCGGAAGTCCTTGACCACTCAAATCAGCAACTTTGATAACATATCAAA ACTTTCTGAGCAAGTTGTGCTCACTAGCATAAGCACACTCCCAGCAGCCAATGGAGCAGG ACCACTTCAAAACTGGTAGAATATTTATTCATATGACAAGGATACCTGAGTAAAACTATC CTTTTTAAAATCACTGGGAACAGAAATTTTATTATCCTATGATGTGAAGCTAAAATTACT AATGATTTCTCAACTTTTGATTTAAATATGTTAGAAGTTTAACCTTCAATTGAGCTTATT TCAGGCTATTTCACTTTTAGTTTCATGTATTAAAATGTGTGTCAATTAAATGTTTAAACA TTTCTAATTCTTTTTATAATCCCTTGTTATTTTAATCTCTCACATTCAGATTGGTTCCTA AAAATTACCAGAATCTATCCAATGATTTTTTTTTTGCTACTAAAAGAAGTAGCAATTACTAA TTTGCAAATTGACCATTGCTAACATTTCTTGTCTCAACATATGGCCAGTAAGACTCTATC ACAGTAAAAGTTTTAACGTAATTTCCATCTCTAACACTTTAACATTTAAGAATAAGCTAA ATCACATCATTATATTCTTTTAACAACAACAACAAAAAGTGATATAGTCAGCCTTGCTGG ATTAAATTAAAAATGCACCACTGTGCTAGGTGCTAGGGAATGAGATGGCGTCGATGCAAA ${\tt CATGCCTTCAAAAGAGCTTCAGTCTAGTGAGGGAGACATGTTGACAGAGTGCAAGGCAGC}$ AAACAATCTGGGGGACAATTCTTGGTCATGGCAGAGCAGTGAAGCTACCAAGGACAGTGG TGACAGTTGATGTCAGTGGATTCCATCTGGGCCTGGGGCTGAGTACCAGGTGGTTAAAAA ATAGAGGGGCTTGCTCTTAACTCACACATACATGAATAGACTATCGTATATTTTGTAGAA AATGTAAGATCTGGGAGTCAAAGCACTGAGTATTCAAACTTATTCCCCTGAAAAATTCTT CTGATTCAAATATTTACTTGAAAATTAAACTAAAAGTAAAAGAAGTGTTTATGAAAGATG ATTTTCATCTCCTATTATGGTAACAGGTGTTCTGATTGTATTGAAACAAAAGATATGGGG CACAGTGTTTAAGAAAACTTTCATAGAAAATTAATTTTTGTTATTTTTTCATTTTTCCA TTACACTCAGAGAAAAGTAAAAGAGCCTAATTATCCACAACTTGTTTTCAAATCTTGGAA TTTGGGATTCTGTTACCTTGTGCCTTTTATGACTCAAAGCAAAAACTATCTTCTTATACA AGGTTTATTGAGATCATATTGTAAAATATCAGCACTATATCAGTGAAAGCAAGGTATTTT AAAGGAGAGTTGTAATTTTCGGATCGTGATGACAGCACTTTAAAAAGTTTGAGGATAACT TCAAATAACGTTGATAATATGCCTTAATAGCCAGTAATAGCTCAGAGGAAGAGTAAATTC GGAAAGGGGGAGAAAAAAAACTGACTCAGAGAGCAGCAGTTATGTGACGTATGGGA AGTCAGAATTCCTTTGCTCTAAATCAGTGATTCTCAAAATGTGGTTTCTATACCATCGGC ATCAGCATCATCTGGGAACTTAGTGGACATGCTAACTTCCACCCTATCCCTCACCTACTT AACCAGAAACTTTAGGGGTGATAGCCCAAAAGCTGTGTGTTAAGCACTACAGGTGTTTCT GAAGCACTTTAAGATTTGAGATCCACTGCTTTAAGTGATACCATCTGACATCAGTTTATC TGCCTGTGTGAAATAAAGTCTTTTACTGCACAGGTGTCTACAACAGGGGCCCACCATCATC GCTACCGTCAACGTGGTTGGATGTCTGAAAGAAGAAGCTGAGTATCAATGTTGACTCTCA CTCATGTCATCTTATTAAAAAAAAAACAGTTTACAAAACAATTGCTACTGATAAATGCAG TGTGAAAGACTGGTTTTAAGGCACTTGTGTGCTTTATGTCCACCCAGATAACTTGAGTTT CAGATAGTTTCTAAGAATGATCATTTCATGGAAGGAGATATAAAATAAAATAAAACCAGT ACTTAAACTCTGGGAATGTAATAGGCCATGTACATAGCACTCAACATGTGAATCCAGGAA TCCTTCTAAGAGGTCTAGATTTAGTATGGTTACCTTAATAGGACAAATGGTAAAGAAATA GGTGTTCCCAAACTCTGCCAATCTTATGAAACAAAGAGTCAACTCTTTACCTCATTATTT GCTAATGACACAAATGCAAAGACATCTTTTGAAAAGAATGTGTTGGGACTGTTTTATGCT GTACCTTGAATGTGTATCTCTCTTTTTTTTGCTATATTTCAAAGATTTAATGTAAGTTGT CAATGTCATTGAGTTCTTGTTATCAATAGGGATGATATAATTTTATCTAACATGGAATCC ATTTTAACTTTGTTATTTCTGAATTTCTATGAAACCACAAAAACCTTCATACTTGAATTT AGCTTGGAGAATTTATTGGATATTAAATACCTGTTATAAATTATTGATGAGTTAATTGCA AGTAGCAGACACATGATATTGAATTTCACTCCCAATACACATTGTTTTAATGAAGATTA AGGTAAATATGTTTATAAAATTTAGTCTGGCTATGCTTAAACCTGAAATAGCAGAATGGC AAAAAACCCCAAAGCTGTTTATGGACCCAAATTGTGAGGAGGGCTATTATTTTAATACTT GTGTAATAATAGAATGCACTTGATGTAAATTGTAATAGCCATCAACTGCATTTCAAAAAC

FIG. 1AN

41/51

CCTTTTCTACTTCTACAAGTCACAAGTCAAAAAAAAAGTAAATTCCACCAAGTTTTATTC AATTAGTTTTCAAATTGCATGAAGCAAAAAATAGATTTTTAGAGACAATATATAAATAGA GCATGAAAACACTATTATTTCCCAAAGTTCAAAGGGAATTGTTTTCTACGCAACTACTG CTACTAACAAGGGGACAACAACCCCCTCCACTTGCCACGTATTTTTATTCTCTTTT ATATCTTTGGAGTTAAATGTCTTTTATGTTTTTCATGAAATGTATTCTATAATTGTTGTA TTTCATGTGTGTAACATTATGTCAGTTGTTTTAACAATTATCTTATATCTTGAAATTCTT TATGCCTGATTGTACTGTGTCTTCATGAAGAAATTTCTTATCAAATCCAATGTGATTACA CACTTACTGCTGTAAAGGATGCGCATTATGTAGTTTTTAAGTAAAAACTATAGTGAGAAT TCTATAATCACATTCACACTCCCCTCTCTATTGTATGAAAAATCTTGTTGTTGTTGATTA GATAAGGTGGATATTCACTCATAGTTAATGTCAAATCTCTGCAGTTAAGGATTGAATTAA GCCCTCTGGTGCAGTACCTAATGATCAAAACATTTTTTCCAATAAGTTTATATAACCAAG GATAATAATGATATAAAAGGTTTTTTAATGTTGTTTTTTAAGAGCAGGTACTATAACAAAGA AGGTTAACACTGGTACAGAAATATTTCATAAAAGTTATGAAAACCAGATAAATACAGTAT TAAATTTTGGAGCTTTTATCTGAGTTGAGAGATTTAGTCTACATTGACTGAGATGAAATG TTTTCTGGGCCATTTTGTATAAGTCATTTAGGACTATTTTAAGTTCACTGGTAAATTTTA AAATGTATATTTTCAGCTTTTCAATTTTTTTCAAAATAGTTCTGAGAAATTACAGAATCA ATAAAAAATGAAGCCAAAGTAACCCGTCAAGGTAAATACTTGACTCCTAGGAAAATGTGA TTTTAGTAGGCATCTCAAGAGGAAGTGAAACTTCTCGTGGTGAAATTACAAGAAAAACAA GTTATTCAGTGGTGAGAATGTGTTGCTCTAAGCAATCCATTAGCACAGACTAGCTACTTG GCCACTCCTCTTCTGGAGCCAGCCCTGAAGAGTGGTCACAGCATCTTCATTTTAT CCAGGCCAATGGCCATGCATGAGAAGTTGGGTAGCAAAATTCTTGAAGCACCTCTTTGTT CTTGCTCTTCTTCACTGTTTTCTCACTCTCCACCTGTAATGCTCACTGCCAGTTTTACC ACCAAGCTAAGTATCAGCAGACCTCCCTCCACAGCGTGCCTTGCCCTGTAGAACTCCTGG TCCTTCCTTCAGCCCAACCCCATCCAATTGCCTAGGTTCTTGTTGTCTCCTGAGATGAAC AAGAGGCAAGTAGCTAATTTGAGAACAAATGAAGCAGAGCTGAAGGAAAAAGTAAAACAT TCCCAGAACATTTATGCTTATCAGTGGTCTTCTGAATCTGTGACAACTCCCTTTTCAAGC CCCAGCTAAGCTTCTTGCCTCAAGCCAGAAGGAATCCCAGTTTTGAGTCTTGTGTTAAGG CCATGGCAGGTCAGTAGGGAGATTATCTGAGGAGGTACCGCTTGTGACACCTTCAGAAAC AAAACAGCTATTGCCTTACGTTTCATAGGCCCAGGCCCTGAGCAATAGCAAAAAGATAAT AATCCTCAGTGCTTGACAACATGAAACTTATTTAACTTATTATAGATGAGATAATGAGAA CATCTTCAGAAAAGAAGCTATGTTCCTTAAAACAGGGGTACAGATTTAAAAGCTCTGTTT ATATGGTTTTGGTAGACTAAGTGAAGAACTTGCCTATAAAGCTGAGTCTCGATCATATAG CATATCCATTATAAAGTGAGAAAATTGCAATTTTAGAGTATTGTCAATACATCCAAAAAT TTTTACATGATTTCTAAATGCAGATGTGTGTGTGTGTATGTCTACGTATGTCTCTCCATA TGCAACAAGCAGTTAATTAGTCCAAATATATCCCACAGTGTAGATTAGTTTCATATCTCA GCTCTTCAATGTCTCTTCTTCATTTAATTCACTCCTTGGTGTCTAGTTTTCCTCACTCTT TTACAAATATCCAGGTTCTATATTTCTGCTTTTCTAGAGAGCTTTTTCCCTCAAGAATAT TATAACAATTTGAGACAAGTGAAAAGGAAAGATCTGTAAACTGCCTATCTCCTTTGAAAT TCATTGCCAATAATCCTTAAGAATATAAAGTTCCTTGATGCCAAAGACCTTCTCATTAGT GTTGCTGCCTGTTGTTTCATTGGTTCCCTAGAACAATGCCTGGCACATAAAAGTTATTTG ATAAATATCTCTGCTATTAATGAATTAATAATAACTGCATGACAATTCTTTCCTCAATTC ATCATTTTGCTTCATTTTCTCACAGTTGCTTCAATGTGTCTGTGGAACTATCTTTCCATG TGAACAAAACACTCTACATTCTCAGTGTCTACAAAGCACATATTTCCTTTTATTAAAATT AAACTTTGAGAGCACCAAATCCTAATGTCTAACCATCAAACTGGCAGATAGCACCAG CTGACACCTGTAAGAGGATTTATCATGGTAAACTTCTCTTTGTTACTGACATTTTCAGCC TCTTGGGCTCTCCCTCCTTACTTATACACATTGGCACCCAGCTTGAAGTCATACTCTCT AGACCCTGGGTCAATGTGGGTAATGCATCCAGGAATCCAGCTTAACTCTTCCTTGGTCTC TTTGATGTGACTGACCTTTATTTCTACATTTCTTCATCAAACCAGTCTCACAGTTTTGCA CAGTGCAAATCACATGCTGCACCATGTGCTTATTATCTCCTATAACAACAGATGCTCCAC

FIG. 1AO

42/51

TGAAATGCAAAACTCTGTGTTAAGCCAACAACTGCTTCTCCATCCTTTCCTCCTATACGT TTCTTCTCACTACAACTTCCCTTCTCAACCCCAAAGGGACTACTGGATTCTTTACTCTTT TACTATTTTGTCCTGATGAAATTCATGACAGTTTTCATACAACAGAAAGCCTGCCCTCTT AGAAGAGAAGAACTGAAAAGAAATGGTTGAAGTAAGGTAGAAAGCCCTCATGGAGTTA GGTGGCTAGGCCAGCAGAGCTAGGCACTGTTCTCCTGTTCAGAATTGCACTCCTGATACT CCAGATGGGAAGCCTGCCATGGCACTAACCACAGCACTTTTTATACCCTATCTCTGCTAT TATGAGCCCACATTAGTTTTCTTCTGCTTCAGAAATTGTTGCAAAAAATAATTTTATTA TTTACAAATTATTTTTAAACCATATAAATCTGCTTAGTTTGATTTCTCAAACCCTCTAAA ACTTACACTTCTTGTTGTCCAATCTTTGCTTTTAATTGGGTATAATTTGAGGCAGAAATA AATTAATCTCATTTTTAAAAATGTACTAGCTATTAATAATTTTTTAAATTTATCTTCTAAA CTTTATTACTTCCATTGAGAACTGTTAAAATAACAGAACTTACCTCACTGTACGCTGGCT TTTGAAAAGGCAGCAGAACTGTTTATCTGATTATCGAAGTAATCATATTACATTTCTTTT TCTTTTCTAAGAGAAACCTTCTTCATGTGCTCAGTCAAACATTTTGGTGTTTAAGAATTG ACTTATTAGGTCAGGCGGGTTGCTCACGCCTGTAATCCCAACACTTTGGAAGGCCGAGG CAGGTGGATCACTTAAGGTCAGGAGTTCGAGACCAGCCTGGTCAACATGGTGAAACCCCA CCCCTACTAAAAATGCAAAAAAAAAAAAAAATAGCAAGGTGTGGTGCACATCTGTAATC CCAGCTACTTGAGAGGCTGAGGTGGGAGAATCATTTGAACTCGGGAGGCGGAGGTTGCAG AAAACACAAAAAACAAAAACAAAACAAAAAAGAGTTGACTTAGTTAATGAAAATATTTTT ATTAGGAAATTATACTTCTCTTTACAAAGTATGTATTATTTGTTGCATCTATATAGTCTA TCAATTCTAAAAGCACACTTTATGCGAAAATGTAGTCTAGGCCTTCAGAATGTATTATTA CAAGAAAGTATCTATCAACCATGTTTCATTTGTTTGCATGTTTTGTTTTGTTTCCAATAG ACTATGAATATTCAGCTTCAAATGCTACCTCATGATTGTTACATTCCTGTTGTTGAAAGA TCATTCCATTGGCAGTAATCTGTGATTCAAAAGTTAACAACATACCATGTATTCTTGTAG GAGATTATTTCATGCTTATCACTGATCAACTTACATGCAGGTTAAAACCAGCCCTGAAAA AATGCTCATCATCACTGGCCATCAGAGAAATACAAATCAAAACCACAATGAGATACCATC TCACACCAGAAGAATGGCGATCATTAAAAAGTCAGGAAATAACACTTGCTGGAGAGGATG TGGAGAAATATGAACACTTTTACACTGTTGCTGGGAGCGTAAACTAGTTCAACCATTGTG GAAGACAGTGTGGCAATTACTCAAGGATCTAGACTAGAAATACCATTTGACCCAGCCATC CCATTACAGGGTATATACCCAAAAGATTATAAATCATGCTACTATAAAGGCACATGCACA TCAATGATAGACTGGATTAAGAAAATGTGGCACATATACACCATGGAATACTATGCAGCC GGAATTGAACAATGAGAACACTTGGACACAGGGTGGGAAACATCACACCCGGGGCCTAT CATGGGGTGGGGGTAGGAGGGAGGGATAGCATTAGGAGAAATACCTAATGTAAATGATGA GTTAATGGGTGCAGTACTCCAACATGGCACATGTATACATATGTAACAAACCTGCACGTT GTTCAGATAACTGGAGCCATCTTCCTAGCTCTTTATTTCTCAGACAGTGTGGGTAAGTCC TGCTCCGTACGAATGCTTATGTCAGTTTTGAAGTTCAGTACTTTCTTAAGAGCCAGAGTC AGTCAAGATGTTCCCTTAACAAGATTTTTCAATGGGGTTACACATTAATGAGTTCTTTTT CCTCCTTTAAGTATTTGAAAATTTTGGTTTAATAAAAGGTTTAACTATGATGAATTTAGG TTCATGTTGCCACTAGGAGTGTCCAGAATAGACAATTGAAACAGCCTTCTAGCTACTACT ATCAAAAAGAGCTTTAAATAACATATTTTAATTAAATAACATTATTTCTATAGCTATA CCTCAATAAAACCATCAACCAATGTTTGTACAATTTGATGCCCCCACTCTAAGATTTTTA GCTAGTGTAAATCAGAGTCTCCTATTTAATGAGACACTTTATCCAATCAGGTTGTGTTTA TTATTCAACCAGATGATCTTGGAACTTATAACAAACTAGTAATACTTAAAGCTGGGCTTT ATGTGCGTGATTTACTGGGATGTTTGCTTATACCTTGTTTCCAAGCTAAAAATATTGTGA CCAGGTGTGTTAGTCTGTTTTGAGTTGCTATATAGGACTACCTAATGCTGGGTCATTTAT AAAGAAAAGAGGTTTATTTGGATTATGGTTCTGCAGGCTGTACAAAGAGCATGACATCAG CATCTGCTTCTGGTAATGCCCTCAGGAAGCTTTTACTCATGCCAGAAGGCAAGGGGAGCC

FIG. 1AP

43/51

GGCACCAAGCCATTCATGAAGGATTTGCCCTCATGACCAAATACCTCCCACTAGGCCCAA CCTCCAACACTGGGGGTCTCATTTCAACATGAGATTTGGAAGGGACGACTATCCAAACTA TATCATCAGGATTTTCTGGCATGGACTACCAAGCCATTTCTGCTTCAAACTCCCCTGAAA TTCTTGTTAAAAATGCAGATTCTTTGATACCACCCCCAATACACTATTTAGTCTGAGATG AAACTCAAGGATTCTGATTTAATTGATCTAGACTAGCATTTGACCATTGATTTATCATCT GGGATTCTAGGAAGTCAACCACTTATATGTTTTAGAGCAGACTTCATTATAATTGAGGAG AATGTTTGTAGTCTGTGGGCTCCTCTGTCCACTTCTGATTGGGGCCCCTTTGCCTGATTC TGACTGGATCAGGCAGAGTTTTATTCAAGCCACTGTCCTTTTTTGGCTTCTTAATGTTCAA AATATATTAACACAATCTCAGTTTTCTAAGAGCTAAATTATACGACTTGGTTCTTGTCTG GTAACATAACTGCATTACTGGATCTTGTCAAGATTCAGAGACATTCTCCCAGTTTCAAAT TTGTAACTAACACTGTTTGATCACAAAAAAGTTCTAAGCCAAAGCAAAACTCTTTCTACC ACCACCAGATGGCGTTACTTTGGACTTACCTATAAATGGATTTCCAAATGGTTTTTCAGA AACCAACTGGAGGTACTTAGAAAAACTTATGGAACTCACAACTATTCTTTGCATGTCAAA TCCTCCAGCTTATTTAAACTATATCCTTATATTAACCCTTGTTGGAGATGTGTCCTCTTA TTGCACTGTATGTGAGTGTGTGTGTGTATCCCATCACGTTGGTATGATGATAGCACCC TTCATTGAGAAGCTTTGCAAAAAGAATATAAGAACATGTTATTATGTTTACTTAAAAGTA TAAGGCCGGGTGTGGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCAAGGTGGGA GGATGACGAGGTCAGGAGTTAGAGACCAGCCTGACCAACACGGTAAAACCCTGTCTCTAA TAAAAAATACAAAAATTAGCCAGGTATGATGGCACGCATCTGTAATCCTAGCTACTCAGG AGGCTGAGGCGGGAGAGTCCCTTGAACCCAGGAGACGGAGTTTGCAGTGAGCCTAGGTGG AAAAAAAGTATTGAGGACATTGCTCATGACATTCCAAGGTTATATAAAAGAATATATAA AAAGAAATTTCTGCCTGGACTTAGTGCCAGGAATACTTGTACTTTCTTGCTTTCTT GAAGGATTAGAGGCAGATCTGTAGCATGCCGAGTCCCATCTTTGCATACAGGCTATCATG ACAAACATTGTATGTGCTAATTCTATCTGGCTTCTCTTTATATTCCTATCTGTCTCTATT TCCTGTCATTTTAATGTTTTAAAATTGTACTTTTACTTAAATGGTTTTTGGAAGAAATA AATATAAGTAAAGTCTGTTAGAGGCCCGGCGCGGTGGCTCACGCCTGTAATCCCAGCACT TTGGGAGGCCAAGGCGGGTGGATCACAAGGTCAGGAGATTGAGACCACCCTGGCTAACAC CGGGTGCCTGTAGTCCCAGCTACTCGAGAGGCTGAGGTGGGAGAATGGCATGAACCCAGG AGGTGGAGCTCGCAGTGAGCCGAGATCTCACCACTGCACTCCAGCCTGGGCGACAGAGCG AAAAGAACGCCAAAGCCAACAAACATATGAAAAAAAGCTCATCACTGGTCATTAGAG AAATGCAAATCAAAACCACAATGAGCCATCATCTCACGCCAGTTGGAATGGTGATCATTA AAAAGTCAGAAAACAACAGATGCTGGAGAGGATGTGGAGAAATAGGAACGCTTTTTACAC TGTTGGTGGAGGTGTCAATTAGTTCAACCATTGTGGAAAGCAGTGTGGCGATTCCTCAAG GATCTAGAACCAGAAATACCATTTGACCCAGCAGTCCCATTACTGGGTACATACCCAAAG ACAATAGCAAAGACTTGGAACCAATCCAAATGCCCATCAGTGATAGACTGGATAAAGAAA ATGTGGCACATATAATATACAGCATAGAACACTATGCAGCCATAAACAAAGGATGAATTC ATGTCCTTGGCAGGGACATGGATGAAGCTGGAAACCATCATTCTCAGTAAACTAACACAG GAACAGAAAACCAAACACCACATGTTCTCACTCATAAGTGGCAGTTGAACAATGAGAACA CATGGACACAGGGAGGGAACATTACACATCGGGGCCTATTGGGGAATGGGGGCTAGGGG AGGGATAGCATTAGGAGAAATACTTAATGTAGATGACGGGTTGATGGGTGCAGCAAACCA CCATGGCATGTGTATACCTATGTAACAAACCTGCATGTTCTGCTCATGTATCCCAGAACT TAAAGTATAATAAAAAAAAAAAGAAAGCACAAAAATAAAAGTACTTGGAAAAGTTTAAA GGGTTAAATATTATGCAAAACTGAAAACTAGCTTCAGATACATTTAAGTTTATATCATGT TAACAAGTTATTTCTTTCTAAAAAATTCTAACCTGTAACACAGAGAGTGGACTTGAACTT GAAAATATGGTTAAGGTACAAATGCAGATTTGGGGTCCCAGTCTCCCAGACTGTGGCTTC TATGGAAGAGATTGTACTGGCTCCAAATTCCACAGATGATTGAACAACTTGTTTCTGCCT GTGTCAGAGCTGAAGAGTGAATATCTCCACTATATATCTCCAAAATCTCCCAAATGAAA TTTGGTAACCCTCTATGCCATAACACATCACATTAATAATTTGTATTCAAAAGTCTCTCA TGAGTACAGATTTCTTACATGCCTATATTGCATAGTGGTGGAGTCTGGGCTTTTACTGTA

FIG. 1AQ

44/51

GTCATCATCTGAACAGTGAACTTGTACCAAATAAGTAATTTTTCAACTCTCATCCACCCA CCCTCCCATCTTTTGTAGTACCCAAGGTCTATTATCCCACTCTGTATGCCTGTGTACCTA TTGTTTAGCTTCCACTTATAAGTGAACACATGCAGCATTTGACTTTCTGTTTCTGAGTTA TTTTACTTAGGATAATGGCCTCCAGTTCCATCTACATGGCTGCAAAAGTTATGATTTTAT TCTTTTTTATGGCTCCATTATATGTATGTGTGTGTTATCTCAATTTTCTTTATCAAACCCT CTGTTGATGGACACTTAGATTAGTCCACATTTTTGCTATTGTGATAAACATGTAAGTGCA GGTATCTTTGTAATATAATGATTTCTTTCCCTTTGGATATATACCAGGTAGTGGGATTTC TGGATCTAATGGTAGTTCTATTTTTAGTTCTTTGAGAAATCTCCATACTGTCTTCCATAA AGGTTGTACTAGTTTACATTTCCACCAAAAGTGTATAAGCATTCCCTTTTCTCTGCATCC TCACAAACATCCTTTGCTTATTGACTTTTTAATAACAGCCATTCTGACTAGTGTGAAATA ATATTTTATTGTGATTTTAATTTTCTCTGATGATTAGTGATGTTTGAGCATTGTCTCAACA TCACTATGCTAGTGGCATGCATGTTTTCTTTTGAAAAAAAGTTTGTGTTCTTTGCCCACA GAAAATTATTCCTTTGTCAGCTGCATAGTTTACAATTTTTTTCCCATTCTGTAGTTTGTC TGTTCACTCTGTTGATTGTTTATTTTTCTGTCCAGAAACTTTAGTTTAAGTCCCATTTGT CTATTTTTGTTTTGTTGCATTTGCCTTTGAGGACTAGGTCATAATTTTTTTGCCTGGGCA AATGTCCTGAAGATTTTTTTCCAGGCTTTCTTATAGTATTTTTATAGTTTCGGGTCTTAT TTTCAATCTTCTACATATGGCTATCCAGTTTTCCCAGCACCATTTATTGAATAGGGAGTC ATTTACCCAGTAAATATTTTAGTTGACTTTGTTAAAAAATCAGTTGGTTATAGGTGTGTGG TTTTATTTCTAGGTTCTCTATGCTGTTCTATTCATCAATGTGTACATTTTTATACTAGTA CCATGTTGTTTTGGTTACTATAGCTTTGTAGCATAATTTGAAGTCATAATATGATGCCAA GAATGATGGTTTCCAGCTTTGTCCATGTCGCTACAAAGGACATAATCTCACCCTTTTTTA TGGCTGCGTAGTATTCCATGGTGTATATGTGCCACATTTTCTTAATCCAGTCTATCATTG ATGGGGGGGGGGGAAGGGATAGCATTAGGAGATATACCTAATGTAAATGACGAGTTAAT GGGTGCAGCACCAACATGGCACATGTATACATATGTAGCAAACCTGCACATTGTGCAC TGGCTTTCTGGACTCTTTTTTTTGGTTTTATATGAATTTTAGGATTTTTTTCTAATTCTA TGAAAAATGGCATTGGTAATTTGATAGGGATTGTGTCGAATCAGTAGACTGCTTTAGACA GCATGGTCATTTTAATAATATTGAATCTCTAATCCATGAGCCAGGGATATTTTTCCATTT GTTTTTGTCATCTAGGGTTTTCTTCCATCAGTGTTTTGTAGTTCTCCTTATAGATATCTT TTACCTCTTTGGTGAAATGTATTCCCAGGCATTTTACTTTATCTTATCTTTTTGTAGCTA TTATAAATGGAATTGCTTTCTTAGTTTTGGTCCTTGGAAATGCCAACTACATTTAAAATCC TTTTCCATTTGATGGATTTCAGGTCTTGATGAACATCTCAGTTGTAATTTTCTTAAGATT GAAAAAGTAAATATTTTTTCTATATGTATATAAAAATTGTCCTCTCAAAAATTTTAAT TCAATAACCTGCTAGATATCACTTTAGAATCTTGCAGTACTAGTTTTCTTCTCAATTAAT TGTAGATCTTAGCCTTTTAATTTGGGCATGTTTTTCCCTATTAGGACTTAAGTTATTAGG ACCTAAGTTTGTAGACAAGAACTATGTTATATTTGAGAAATTTGTGAGTCATGTACTGGG CCTAGCACAGTGCCTCATAAGATGTAGACCCTCAATAAACTTGTTGAATAGGTTAATAAA CACCCAGCCTGGAGTGCAGTGGCACGATATCGGCTCACTGCAAGCTCTGCCTCCTGGGTT CACACCACTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGACTACAGACACCCGCCACCATG CCCGACTAATTTTTTGTATTTTTAGTAGAGACGGGGTTTCACCTGTGTTAGCCAGGATGG TCTCGATCTCCTCACCTCATGATCTGACCCCCTCGGCCTCCCAAAGTGCTGGGATTACAG GCATGAGCCACCACCTGGCCTATTTCAGTCAATTGTTAAAAGTGCTAAGAACAAGTGG AGATCTTGTTAATGAAGAAAAAAAAATAGTATTTACTACTTACCTAAACACTCTACTAA AAGAAGAACGTAAACAAAGTCAAAAATGCATTTTTTAGGTGCTAGAGATTAGACAGGACA AAATCTTCTGGCTCTGCCTAGAGTTAAGTGGCTTTGGGAGAGGCTTTGCTGTAGTTTAAA GGCAGAGGTGGGGAAGGCCACTCTGGCCACAAGGACAGATCCACAATGGGATGGGGTATG AAACAGCACGAACCCTTCAGGAAATTACACATAATTTAAAAGGAAAATGGGAGCCCATGG CAGAAAATAGAATTGAACAGCAGGAAAAGGGTAGATAGTAAAAAGCATTTTATAATATTC AAGGACATTTGAAACTTGTGGTATACAATGAGGAAGAATTTAAAAATTCTATACAGAGGA GTGACATAGTTAGATTTGTGTTCTGGGGAGCATAATAATAGCATTACAGCGGGTGAATTT GAAAGCTGGGCCTCAAAAGTTTAGATCTCAAATAGGTTTTTATGGGAGTATTCATCCTCA TGAAACATGATTTGGAACTAAACCAAGGCAGTGGCAATGGGGCTGGAAAATAAACACTAG

FIG. 1AR

45/51

ATTTCATATCTAGATGAAGATTTGTGGAATAAGAGAGGCCACATTAATGTTTAATTCTAT TTACAATGGATCCCAGCCACCATCCGCTTTAACACAGAGGTGCTTTTCCAGTAGCTAAGA GGACTAGGTGCTTTAGATACATTTGTGAAGTTGTCCTCCCATTGTTAACATGCTTTTTTT ATTGTCTGTGTGTGGGGTTGATGGGGGGGGGGGGGGGTTAGGATCACACATAGAAGTTCAGTC TTTGAAATGCTTTCTCTTTTTTCCCCAAACAATGACCCCCACCTTTTCCTTCTGGCA TATGTTGCCTCAAGACCCTAACACTGCTGCCAATCTGCTGGTCTTAGAGCCAAGAATCTG CCACCACCTGGCCCACCACAGCCTGCTCTGCTAGCTGCTCTCCTGCCAATACTGGCCTTC ATGTACAAGTGTAGGTTTTGAGGGTTCCGTTCTCTCCCCCTTTCTCTCTTTGAGTGTGGG TTTGTGAGTGTGTGTCTTCTGTAATAAGAAGAAAACAGGCCACATTTTCTCTACTCGT GTTATACACTTCCCGGAGTGTCTCACATCAAAACCTGTCCTAAGTCCAAGCCTTAGAAGC TCTTTGCTGGCCCAGCCTACACTTGGGTTGTTACTTCTCAGGAGCTACCTTTCTGTCAGT TGAGATTTTAACAACCCACCACAGTACTCCAAGCGTGCAGTCCCTCACATCTTGAAATCT GTGCTTTGGCAGCAGCAGAATCAGGGGTCTGTGGATTCTGAACCCAGAATGTGTCAAACC AAAGGGTGACATATTGGGACATTTAATAAGTCAGAGACTATTTCCCAGGAATATTTTTTT GAAGCATTTAAACTAAAATACAATTGAACTGAGATCTCAAAACAGGAAAAATGAACTTGA CAAGAATTAGGCTAAGCTGCATCTCATGACGTAAATATTCACATTTGCATATACATTAAC AGAGTCAAGTCAAAATTGATTTTTTTTTTGGATAGGATTAACTTTAGCTACAGAAAACAG AAAGTTTAAATGACTGGCTTTAAAAAGCAAAAGTTTACTTGCTTTCATTTATATGCAATC TGGGGGGTTGCGGGAAGATTTGTTTGTGGGTTTCCCATTCTCAAGGTGCCAGGCTCCT GTGTTTCTGCCCCATATCCTTAGAGGGAGGGTTTCCTCCTCAGGATTGCCTTATGTGCAA AGGAACAGAAAGGCACATGACATCACTTCAAATAAAATTAGGGGGGAAAATAATAACAGAT TTAAGATCCTTGAAAACAAGGAGTAATAGTTGAGGAAAAGCTTCTTAGCAGCCTGGGACT AAAAACTTCAAAAAATTTAAGATAAAAATCTGAAAACTGGTAGAGAATTGGGGAGAAAAA GAGAATTTGAACAAGGCATGCAAGAGTAAGAAAATGTCATCACAAAATTACTAAGAAAG CATAAAAGCAACTATATTTATTAGAGTAAAAATAAATGGATTGAATAACCCTAGTAAAA ACTAAATTTAAGTGCAAAGATCTCCCAGGGAAGTCAAAGCAAAAATAAAGTCAGATGTTG CTGTCATTAGACAAAGTAAAATTTAAGGTGAAAACATGACAAAGAGGGACATTAAATAAG GATAAATGTACAATCAATGGTGACAAACTTTTATAAACTTGAAATTATATTAACAAAACA TAAATCATGTAAAACTAAAATACCTTGATAAAATGCAAATTATCAGGTAACAAGAATATA TCTATTGCAGAAAGTAATATATCAAACTAAAATAATGTGTATCTATTACAAGTATACAAT ACTTTGTAGCCTACAAAATAAGAATATACGATTTCTTCTTAAAATGTTATACATTTACAA TAATTAATAATTTGGCCACTCAGAAAACCTTGGTAAAGCAAGGAAAGTAGAGATATTATA AGCCAACTTAATAATTTAGTAACATTGGGTAAAAATGGAAGAAGTATCATATTGTGGTTG TGAACATAAGCTCTAGTTCTCCTAGTTTTGTGATTTGGGAAAGTTAATTATCTTCTCTCT ACCTCGTCTTAATTTTCAGTAATATTAGGATAACAATAGTTTGTACATCATCAGTGTTTT TTTTTTTTGAGGAATAAATGACTCACATGTATTAAACACTTAGATCCATTGTTAACATAT AATATGTATAAATAATGTCAGTATAAATCAATGTCAGCCTAAAAAGTTAAGACTGTGATT TTAAATAATACTAGATTTAGAATAAAATCAAAATTGAAATGACATTATTAACTTAAAAAT AACAAAAAAAGAGAAGACTTTAAACACAATGGATGGAAAGCAGCTATACCAATAAAAGAC AAACATAGAATTTTAAAAATTAAATGTTGGAGGGATTAGGTCAGATAAGAGAAATTTCTG TTAGCAGCAGCTGAATTTCTGCTAATAACAGAGAATTGTGAAAAGATGATTTCATAAAT ATGGCAAATGTTTGTAATAGCCATCCTAGGAGCACGGATATTAGTAACTAATTGAGGAAG TACTGTTGGGCAGTGTCAATATACTGGTTAAGAATAGAATTTAAAATAATGCTAATTATA AGGCCAAAAAACTCAGTAATGCAATTTTTTTTAGTATAATTCAGTAGGGGAGAAGGAGAGA TAATTAAACTTGGAAATTGACATACAGTTGTCCCTTGGCATCCATGAGGAATTAGTTCCA GGACTCCCTATGGATACCTAAATTCACAAATGCTCAGGTCCCTTATATAAAATGGCAAAA TATTTGCATATAACTTACACACCCCCCTCTTTATAATTTAAGTCATTTCTAAAGTACTTAT AATACCGAATGCATTATAAATGACTGTGGAAATAGTTGTTGTATTATTTAGGGAATAATG TTGATCCACAGTTGGCTGAATCTATGGATACAGAGCCCACATTTACTGAGGGCAGACTAT ATTTAGAGTACTTAAGGATCACAAGGGACACACATCTGAGGGTACTGAAGAGTGGGAAGA AATTACTAACCAGAGGGTCAGACTAGAAGGCAAGGAAGTGAAGCCAGGAGATGATTAGAA AATAAGAAAATCATACAAGCCTGGAGATTATGTTGAAGTGTAAGAACATAATTAGAGTGA

FIG. 1AS

46/51

GAAACATGAGTCAAGGAAGAAGGAGATTGGTGCTTGAGAGATGTGGCAGACTGTATCTTT CAAAGATGGCTACACCAATATATATCTCATTCCACAAGCTGTTTTTACCATGCTGTATTG TAATTGCCTTGATCAACAGATTGCAGTAGGAGTGATGCTGGATGATTTCAAAGGCTAATA CACACAAGAAAATAATGGCTTTCATTTGACTCTTTCTTGGAACATGTGCCTTGGAAACCA TGAGCTTATTTGCAAGAAGCTCAGCTATCCTAAAGTTTATCTACTGGGTAGACCAAGTGG AGAAATTACACAGACATTGAGATTATGTTCAAGGGGTCTCAGAGGTTCAAGGCCTCCCAA TTCAGGCACCAAACAAGTGGAGAAAAGGCTTTCAAGATCATCCCTCTGAAATAATTGTCT GATTGAAACCTCAAAAGAGTCCCTGAGCCAGAACCATCCAGCCAAGCCACTCTCAAATTC CAAATCCACAGACACCATGAATGACAGTAAATCATTATTGTTGTTTTAAAGCACATAAGT TTTGGGGGGTTATTTACACACAGCAACAGAAAAAAAAACTGATGAATGGGAAACATGGAG AGAAATGCAAATAGAATAAAATGGGAAGGAATACAAGGAGAGGAAAGTAGTATTGTGCAA AGGTCAGATTAAATTGGAAGGTAACAGGTACAAATATCATTAATGCTAAATTCTATTTGT AATTTATTTAGAAATCTATAGAAGAAGAAAAAGAATAAAAGCCATTGGAAAAGTTTTTAC AATTATTCCATTAAATAGACAAAGTCCTTTAAGGAAAGGGATTAAAATGAAGGTAAGGTG ATCTGCTTAAAAATAATATAGCAATCTGGGAGCCATGGCTCATGCCTGCAATCCCAGTGC TTTGGGAAATCTAGGCAGGAGGACCTCCCAAAGGAGGACTTGGAGTTTGAGACCAGCCTA GAAATAATATTGTATTAATTCCAGTAAAAGCATCAGACCAATTTAGAATATGGATGAGAG AGAAAAACTAGAAATAACACCACAACAAGGAAGGAGAAAGCTGGTCTCTGGCAGGGACTT CTAATTTAGAGAAAGACAGATGATAGCAAACAGCAAAAGTTGTATTATAGATGTAACTTA AAAACTAATTTGATTTTTATTTTTAGTCAGAAAACTGCTTTAGGTATGGAACAAGTATAA $\verb|CCTGGTATTTCCAGTATCTCTGTTGACCTCACATCTCTCCAGATACTGCCTCAATT| \\$ CTCTGCTTCTCTTTATAGCAAATTCCCTTGAAAGAGAGACTACCTGGATCAGAAATTCCT CTGCTTCAATTTGATCCTGAATCCACTTCATCTAGATCTTCCTCACCAATTCCCCCAAAT ATTTGTCTTATTATGGTCACATGGGACCTCTACTTTGCTATATCAGTAATTTTGTTCTCA TTTTACTTTTTTGTAGTTAATTACTCCCTTCTCCTTGAAACACTTTCCTTGTTTGGCTTC CAATATCTTCGTGATCTTATATTTTTAATGCGTCCTGCTAGCTTCCCAACTAGGTTTCCT ACTTTCACCTTAATTCCCTATGGTTTATTCTCTACAAGAAAGGAATTATAATCCCTTAAA AATGTCAATAAAACTCTATCACTACTCAATACTCTCCAAGGGGTCCTTATTTTATTCAAG TAAAAAACTAAAGTCCTTACTATATGTCTGTAAATTCCCATAGGATCTGGCCCCACAGCC CCTCTGGCCCCTGTCCATTCTGCCCCTTGCCAATTCTGCCCGGCCACAGTTGCCCAATAG CTGGTCTGTGAACACATCAAGCACATACTTAATCTCAAGGCTTTTGCAATCATTCTTTTC TCTAGTTGTAATCTCTCATTACTTATTCTGAGTGTCTTGTTTCTGCAGTTGCTTTACTTA CTTGACCTATATAAAATAGTAATTCTTACCCCTACAACTCCATTATGTCCTATCTTCTTT GCCTTGCCTTATGTTTTTTTTTTGGAGTTACAGATACCTGATGTAGATAGTATTTACTTT TTTTATGCTTGCATTAATCACCTAGAATATAAACTCCAAAAGAGGGGCTATTTCTCTTTT ATAATCTATCTAATATCTTGGATATTTGCTCCCACCTAAATTTCATGTTGAAATGTAA TTCCCTGTGTTGGAGATGGGGTCTGGTGGGAGGTATGTGGATCATGGGGCGGATCCCTCA TGAAGGGCTTGGGCCATCCTTTTGGAGAGAGTGGGCTCTGGCTCTGACTTCACACGAGA TCTGGTTGTTTAAAAGTGTGCGACAGCTCCCCTGAGCTTCCTCTCTCACTTGCTCCTGCT TTTGCCATGTGAAGTACCAGCTACTGCTTCATTTTCCACCATGAGTAAAAGATCCCTGAG GCCCTCCCTCAGCAGTACATGTCCCTATGCTTGTTGTGCAGCTGGCAGAACCATGAGCCA ATTAAATCTCTTTTCTTTTAAATTACTCAGTCTCATGTATTTCTTTATAGCAATACAAGG TTGGCTTAATACATATCTCTAAAGCAAAAGCTGGGCCTGGTATGTAATAGGTGTTCAATA AACACTGGGTAGATGTCAAGATGACAGTTTTGTTATTCACATATGGACATGGAAAGGTCT TTGTGGTGCATTGTTAAGGGAGCAAACCAAATTACAGAACACTATATAGAGTAGAGCTGT ATAAAATACATATGGTGTATGTTTATAAATATGTCTAGAAAAATTTGAAAGCTATATATC AAATATCATATCATTTATCTTTAGAAGGCTAATTGCATATTTTCAATTTATTGTTTATAA TTTTTTTTATCTATTATTATAGGTTACTTGTATAATCACAAAAGACAACTGAATAATTCT TTTTGTCTTCATCAACTTTTATTTTAAGTTCTGGGATACATGTACAGGATGTGCAGGTTT GTTACATAGGTAAACGAGTGGCATGGTGGTTTGCTGCACAGATCGACCCATCACCGAGGT ATTAAGCTCAGCATCCATTAGTTATTCCTCCTGATGCTCTCCCTTCCCCTTGGCCCACCAA

FIG. 1AT

47/51

TACACCCTAGTGTATGTTGTTACCCCTCATGTGACCATGTGTTCTCATCATTCAGCTCCC CCATATAAGTAAGAATATGCAGTGTTAGGTTTTCTGTTCCTGTGTTAGTTTGCTGAGGAT AACAGGTTCTAGATCCATCCCTGCAAAGGACATGCTCTTGTTCCTTTTTATGGG TGCATAGTATTCCTTGGTGTATATGTACCACATGTACAACTAATTTCCACAACAAAAAAT GTACTATTACATGGATATAATGTTTATATTCTCTTCACAGAATTTGAGTCACTTGAATTT CCAATAAGTAAATGTGGAAGGTTGGTGGAAATAGTTAGCTGGAAACTCAGAATTGATATT GCACTATCTATGCATTCAAACAATGATACATATGGTGCATATGTATATATGGCAAAAATC TAAGAAATGTAGCCAAATATTAATATTGCTTACACGTAAGTAGTCAAATCATGGTGGTTT TTTTTTATTTTCTTGATTTTTGCAAGAAAATTAATAAAGAGGCTATTTACATTTTAATGTA AACATTTCTGAATTTTTTAAAGATTTCTCAATAGATCTAGGTATTCTTCTTAACCAAATA CTGATACTACCGTTAACCACTTCTGGAAAATTCTGGCAATTGGTCCCTTTGGGGAAGAAC TAGAGGAATCACTATACACACTTACTGTGGTATTCAGTGCCCTTCCTCAAGGGGAAT TCGCCTATCTTTTTTTTCTTAAGTAATATTTTATCTTTAATAGACAAATAATGGTTGTAT TTATTTACGGGATACAAAGTGACATTTTGATGCAAGCATACCTTGTGGAATGATCAAATC AGGCTAATTAACATATCTGTCATCTCAAATGCTTATCCTTTCTTCATTGTGGGAGCACTT AAAATCAATTCTTTTAGCTATTTGGAAATATAAAATATATTATTTTCTAACTATATTTAC CTCTTTGACCAACATCTCCCCTTTCTTTGTCCATCCTCCTAGCCCAGCCTTTGGTAGCCA TCACTGTACTCTGTATTTCTATCACTTTGCCTTTTTAAATTGCACATATAAGAGAGATCA TGCAGTATTTGTTGCTTTGTGTCTGACTTATTTCCTGTAGCAGAATGTCCTTTAGGTTAA TCCATGTTGTCATAAATGACAAAATTTCCTGCCTTTCAAAGGCTGAATAGTATTCCATTG TTTATATATACCACATTGTCAAAATCCATTCATCTGTTGATGGGCATGTAAGTTGTTTTC AAATATTGGCTTTATTAATAATGCGGCAGTGAACGTGGGAGTTCAGACATCTTGTTGACA TACTGATATTAATTCCTTTGACTATATACTCAAAAGTGGAATTGCTGGACTGTGTGGTAA TTTTAGATTTTTAGTAACATTCATACTGTTTTCCAAAATAACTGTATGAATTAACAATAC CATCAACAATGTACAAGGGTTCCCTCTGCTCCACATCCTCATCAACACTTGCTAGTTTTC ATGTTTTCGATAATAGCCAGTCTATCAGGTGTAAGATAATATTTCATTGTGATTTAATTA GCATTTCTTTGATAATCAGAGATTTTGAGCCTTTTTTAATATCTGTTGACCACTTTTA TGTTTTCCTTTGAGAAATGTGTATTTAAGTCGTCTGCCCATTTTTAATAGGATCATTTGT TTTCTTATTATTGAGGGGTTTGAGTTCCATGCATATTTTAGATACTAGCCTTTTATCCAA TGCGTAATTTGCAAATATTTTCTCCCAATCTGTGGGTTGTCTCTTTAACCTGCTAACTGT TTCCTTCCTGCAGAAGCTTTTTAGTTTGATGCAATTCCATTTGTCTATTTTTGCT TCCATTGCCTGTGCTTTTGGGGTTAAGAAATCTCTGCTCGATTACATTTATTGATTTGCG TATATTGAACCAGCCTTGCGTCCCACGGATGAAGCCCACTTGATCATGGTGGATAAGCTT TTTGATGTGCTGCTGGATTCGGTTTGCCAGTATTTTATTGAGGATTTTTGCATCAATGTT GAATAGTTTCAGAAGGAATGGTACCATTCCTCCTTGTACCTCTGGTAGAATTCGGCTGTG AATCCATCTGGTCCTGGACTCTTTTTGGTTGGTAAACTATTGATTATTGCCACAATTTCA GAGCCTGTTATTGGTCTATTCAGAGATTCAACTTCTTCCTGGTTTAGTCTTGGGAGGGTG TATGTGTCAAGGAATTTATCCATTTCTTCTAGATTTTCTAGTTTATTTGCGTAGAGGTGT TTGTAGTATTCTCTGATGGTAGTTTGTATTTCTGTGGGGATTGGTGGTGATATCCCCTTTA TCATTTTTATTGTGTCTATTTGATTCTTCTCTCTTTTTCTCTTTATTAGTCTTGCTAGC GGTCTATCAATTTTGTTGATCCTTTCAAAAAACCAGCTCCTGAATTCATCCATTTTTTGA AGGGTTTTTTGTGTCTCTATTTCCTTCAGTTCTGCTCTGATTTTAGTTATTTCTTGCCTT GTGTCAGTTTTGGATCTTTCCTGCTTTCTCTTGTGGGCATTTAGTGCTATAAATTTCCCT CTACACACTGCTTTGAATGTGTCCCAGAGATTCTGGTATGTTGTGTCTTTTTTCTCGTTG GTTTCAAAGAACATCTTTATTTCTGCCTTCATTTTGTTATGTACCCAGTAGTCATTCAGG TCTAGTTTGATTGCACCGTGGTCTGAGAGACAGTTTGTTATAATATCTGATCTTATACAT TTGCTGAGGAGAGCTTTACTTCCAACTATGTGGTCAATTTTGGAATAGGTGTGGTGTGGT GCTGAGAAGAATGTATATTCTGTTGATTTCGGGTGGAGAGTTCTGTAGATGTCTATTAGG TCTGCTTGGTGCAGAGCTGAGTTCAATTCCTGGATATCCTTGTTAACTTTCTGTCTCGTT

FIG. 1AU

48/51

GATCTGTCTTATGTTGACAGTGGGGTGTTAAAGTCTCCCATTATTATTGTGTGGTAGTCT AAGTCTCTTTGTAGGTCACTCAGGACTTGCTTTATGAATCTGGGTGCTCCTATATTGGGT GCATATATATTTAGGATAGTTAGCTCTTCTTGTTCAATTGATCCCTTTACCATTATGTAA TGGCCTTCTTTGTCTCTTTTGATCTTTGTTGGTTTAAAGTCTGTTTTATCAGAGACTAGG ATTGCAACCCCTGCCTTTTTTTGTTTTCCATTTGCTTGGTAGATCTTCCTCCATCCTTTT ACTTTGAGCCTATGTGTGTCTCTGCACGTGAGATGGGTCTCCTGAATACAGCACACTGAT GGGTCTTGACTCTTTATCCAATTTGCCAGTCTGTGTCTTTTAATTGGAGCATTTAGTCCC TTTACATTTAAAGTTAATATTGTTATGTGTGAATTTGATCCTGTCATTGTAATGTTAGCT GGTTATTTTGTTTGTTAGTTGATGCAGTGTCTTCCTAGCCTCTATGGTCTTTACAATTTG AGCTCTTTTAGGGCAGGCCTAGTGGTGACAAAATTTCTCAGCATTTGCTTGTCTGTAAAG GATTTTATTCTCCTTCACTTATGAAGCTTAGTTTGGCTGGATATGAAATTCTGGGTTGA AAATTCTTTTCTTTAAGAATGTTGAATATTGGCCCCCACTCTCTTCTGACTTGTAGAGTT TCTGCCGAGAGATCCGCTGTTAGTCTGATGGGCTTCCCTTTGTGGGTAACCCGACCTTTC TCTCTGGCTGCCCTTAACATTTTTTCCTTCATTTCAACTTTGGTGAATCTGACAGTTATG TGTCTTGGAGTTGCTCTTCTCGAGGAGTATCTTTGTGGCATTCTCTGTATTTCCTGAATC TGAATGTTGGCCTTCCTTGCTAGATTGGGGAAGTTCTCCTGGATAATATCCTGGAGAGTG TTTTCCAACTTGCTTCCATTCTCCCCGTCACTTTCAGATACACCAATCAGACGTAGATTT GGTCTTTCACATAGTCCCATATTTCTTGGAGGCTTTGTCCGTTTCTTTTATTCTTTTT TCTCTAAACTTCCCTTCTCACTTCATTTCATTCATTTCATCTTCCGTTACTGATATCCTT TCTTCCAGTTGATCGCATCGGCTCATGAGGCTTCTGCATTCTTCACGTAGTTCTCGAGCC TTGGCTTTCAGCTCCATCAGCTCCTTTAAGCACTTCTCTGTATTGGTTATTCTAGTTTTA CATTTGTCTAAATTTTTTTCAAAGTTTTCAACTTCTTTGCCTTTGGTTTGAATTTCCTCC TGTAGCTCGGAGTAGTTTTATCGTCTGAAGCCTTCTTCTCTCAACTTGTCAAAGTCATTC TCCATTCAGCTTTGTTCCATTGCTGGTGAGGAGCTGCGTTCCTTTGGAGGAGGAGAGGTG CTCTGCTTTTTAGAGTTTCCAGTTTTTCTGCTCTGTTTTTTTCCCCATCTTTGTGGTTTTTA TCTACTTTTGGTCTTTGATGATGGTGATGTACAGATGGGGTTTTTGGTGTGGATGTCCTTC CTGTTTGTTAGTTTTCCTTCTAATAGACAGGACCCTCAGCTGCAGGTCTGTTGGAGTTTG CTAGAGGTCCACTCCAGACCCTGTTTGCCTGGGTACCAGCAGCGGTGGCTGCAGAAGAGC GGATTTTCGTGAACCGCGAATGCTGCTGTCTGATCGTTCCTCTGGAAGTTTTGTCTCAGA GGAGTATCCTGCCGTGTGATGTGTCAGTGTGCCCCTACTGGGGGGTGCCTCCCAGTTAGG $\tt CTGCTCGGGGGTCAGGGGTCAGGGACCCACTTGAGGAGGCAGTTTGCCCGTTCTCAGATC$ TCCAGCTGCGTGCTGGGAGAACCACTGCTCTCTTCAAAGCTGTCGGACAGGGACATTTAA GTCTGCAGAGGTTACTGCTGTCTTTTTGTTTGTCTGTGCCCTGCCCCCAGAGGTAGAGCC CACAGAGGCAGGCCTCCTTGAGCTGTGGTGGGCTCCACCCAGTTCGAGCTTCATGG CTGCTTTGTTTACCTAAGCAAGTTTGGGCAATGGCGGGCACCTCTCCCCCAGCCTTGCTG CCACCTTGCAGTTTGATCTCAGACTGCTGTGCTAGCAATCAGCAAGACTCTGTGGGCATA GGCCTCTCCAGCATATAAACAGAACCAAAGACAAAAACCATATGATTATCTCAATAGATG CAGAAAGGGCCTTTGACAAGATTCAACAACGCTTCATGCTAAAAACTCTCAATAAATTAG GTATTGATGGGATGTATCTCAAAATAATAACAGCTACTTATGACAAACCCACAGCCAACA TCATACTGAATAGGCAAAAACTGGAAGCATTCCCTTTGGAAACTGGCACAAGACAGGGAT GCCCTCTCACCACTCCTATTCAACATAGTGTTGGAAGTTCTGGCCCAGGCAATTAGGC AGGAGAAGGAAATAAAGGGTATTCGATTAGGAAAAGAGGAAGTCAAATTGTCCCTGTTTG CAGATGACATGGTTGTATATCTAGAAAGCCCCATTATCTCAGTCCAAAATCTCCTTAAGC TGATAAGCAACTTCAGCAAAGTCTCAGGATACAAAATCAATGTACAAAAATCACAAGAAT TATTACACACCAATAACAGACAAATAGAGAGCCAAATCATGAGTGAACTCTCATTCACAA TTGCTTCAAAGAGAATAAAATACCTAGGAATCCAACTTACAAGGGACGTGAAGGACCTCT ACATTCCATGCTCATGGTTAGGAAGAATCAATATCGTGAAAATGGTCATACTGCCCAATG TAATTTATATATCAATGCCATCCCCATCAAGCTACCAATGACTTTCTTCACAGAATTGG AAAAAACTACTTTAAAGTTCATATGGCACCAAAAAAAGAGCCCGCATCACCAAGTCAATCC TAAGCCAAAAGAACAAAGCTGGAGGCATCACACTACCTGACTTCAAACTATACTACAAGG CTACAGTAACCAAAACAGCATGGTACTGGTACCAAAACAGAGATATAGCTCAATGGAACA GAACAGAGCCCTCAGAAATAATGCTGCATATCTACAACTATCTGATCTTTGACAAACCTG AGAAAAACAAGCAATGGGGAAAGGATTCCCTATTTAATAAATGGTGCTGGGAAAACTGGT TAGCTATATGTAGAAAGCTGAAACTGGATCCCTTCCTTACAGCTTATTCTAAAATTAACT CAAGATGGATTAAAGACTTAAACGTTAGACCTAAACCATAAAAACCCTAGAAGAAAACCT

FIG. 1AV

49/51

AGGCATTACCATTCAGGACATAGACATGTGCAAGGACTTCATGTCTAAAGCACCAAAAGC AATGGCAACAAAAGCCAAAATTGACAAATGGGATCTAATTAAACTAAAGAGCTTCTGCAC AGCCAAAGAAACTACCATCAGAGTGAGCAGCCAACCTACAAAGTGGGAGAAAATTTTCGC AACCTACTTATCTGACAAAGGGCTAATATCCAGAATCTACAATGAACTAAAGCAAATTTA CAAGAAAAAACAACCCCATCAAAAAGTGGGTGAAGGATATAAACAGACACTTCTC AAAAGAAGACATTTGTGCAGCCAAAAAACACATGAAAAAATGCTCATCATCACTGGCCAT CAGAGAAATGCAAATCAAAACCACAATAAGATACCATCTCACACCACTTAGAATGGCAAT CATTAAAAAGTCAGGAAACAACAGGTGCTGGAGAAGATGTGGAGAAATAGAAACACTTTT ACACTGTTGGTGGGACTGTAAACTAGTTCAACCATTGTGGAAGTCAGTGTGGCGATTCCT CAGGGATCTAGAACTAGAAATACCATTTGACCCAGCCATCCCATTACTGGGTATATACCC AAAGGACTATAAATCATGCTGCTATAAAGACACATGCACACGTATGTTTATTGTGGCACT ATTCACAATAGCAAAGACTTGGAACCAACCCAAATGTCCAACAATGATAGACTGGATTAA GAAAATGTGGCACATATACACCATGGAATACTATGCAGCCATAAAAAAGGATGAGTTCAT GTCCTTTGTAGGGACATGGATGAAATTGGAAATCATCATTCTCAGTAAACTATTGTAAGA ACAAAAACCAAACACCGCATATGCTCACTCATAGGTGGGAATTGAACAATGAGAACACA ATAGCCTTAGGAAATATACCTAATTATAAATGACGAGTTAATGGGTGCAGCACCAGCA TGGCACATGTATGCATATGTAACTAACCTGCACATTGTGCACATGTACCCTAAAACTTAA AAAAATAAAAAGAAATCTCTGCTCATATCCAGGCCATGATGGTTTCCCCCCTGTGTTTTCT TCAAGTAGTTTTATAGCTTCAAGTCTTATGTTATATTAAGTCTTTAATCCATTTTGAGGT GTTTTCCCAACACCATTTATTGAGAAGTCTGTCATTTCCCCATGGTGTGATCTTGTTACC TTTATGAAAATTTAATTGACCATAGGTGTATGGGTTTATTTCTGGGCTTTCTATCATATT ${\tt CCATTGATTGATATGTCTGGTTTTATGCCAGTACTATGCTGCTTTGATTACTGTGGATTT}$ GTAATGTAATTTAATGTCTGAGAGTGTGAAGCCTGCAGCATTATTTTTTCTCAAGATTGT TATCTGTGGCTATTTGTAGTCTTTTGTGGTTTCATATATTTTTACAATTTTTTATTTCT GTGAAAAATGCATTGGAATTTTCATATGGATTACATTTAATCCGCTTTGGGTAGTATGAC GTCATCTTCAGGTTTTTTCAACAATGTTTTATAGTTTTAGTATATGGATCTTTCACTTCC GTGTGTGTGCATCAACTAACCATAGTCATGTGGGTTTATTTCTGGGCTTTCTATCATGTT ACTGTTGTAATTTTAAAATTTCTTTCTCAGGTTGTATGTTGTTAGTGTACAGAAATAATA TTAATTTTGTAAGTTGATTTTGTATTCTGCAAATTCACTAAATTTGTTAATTTGTTTTAA AATTTCATTTATTCTTTTCCTATTTGGATGCTTTTTATTCTTACCCAATTGTTTTGACTA GGACCTCCAGTACTATGTTGAACATAATTGATGAAAGCAGACATCCTTGTCTTGCTCCTG ATCCAAAAGCCTTTAACTTTTCACCACTGAGTATGATGTTCACTGTAGGCTTGTTATATA TGGTCTTTGTTGTGCTGAGAAACATTCCTTCTATAACTGATTTTCAAAAGTTTATCATGA AAGGATGTTAAATTATTTCAAATGTTTTTTTTTCTTCATCTATTGAGGTGATTATATTGTTTT TATTCTTCATTCTGTTACTATGGTGAATCATATTTTTAATTGTTTTTTACTTGCATAAAT TTATTTTGTGATAGGTAGAAAAGCACATCTGCAGACCTAGAAGCAGAGTGAATCTAAAAA ATATTATTATAATTATTATGAGTACACAATAGGTATATTTTTCATGGGGTACATTCAA TGTTCTGATACAGGCATATGATGTGTAATAATCACATCAGGGTATTTGGAGTATTCATTA CCTCAAGCATTTATCATTTCTTTGTGTTAGGGAATTTCAGTTTCATTCTTCTAGTTATTT AAAATATACAATGAATTATTATTGACTGTAGTCACCCTGTTGTGCTATCAAATAGTATGT CTTATTCATTTATTTAACTATATTTTTGCACCCATTAACAATCCCCACTTGATTTGAAT ATGGTAAGCCATTCTTGCATCCTAGGAATAAATTCCATTTGACCATGGTGAATGATCCTT TTAATGTACTGTTGAATATAGTTTTTGGTATTTTGTTGAGGATTTTTTGCATCCATGTTCA TTGGTGTGCTGCACCCATTAACTCATCATTTAACATTATGGAAAATCTCCTAATGCTATC CCTCCCGCTCCCCCACCCCACAACAGGCCCCGGTGTGTGATGTTCGCCTTCCTGTGTC CATGTGTTCTCATTGTTCAATTCCCACCTATGAGTGAAAACACACGGTGTTTCTTAGTCT GGCTTTGGTCTCAGGCTAATGTTGGCCTTACAAAATGATTGTGGAAATATTTCCTTCTCT TCAATTTTTTGAAGAAGTTTGAAAATAATTATTACCAGTTCTTCTATAAATGTTGGGTAG

FIG. 1AW

50/51

AATTCATTTATGAAAATATCTTTTCCTGGGTTTTCCTTGATGGCGGACTTTTCATTACTG ATTTAATTTCCTTGCTCATTACTGTTCCATTTATATTCCTCATGATTTGATCTTGGAAGG TTCGTAGTGGTCTCATAAGATCCTTTGTATTTTTGTACTATCAATTGTGATATCTTTTTT CATTTCTGCTTTAGTTTACTTGAACCACCTGTATTTTCTCGTGGTTAATTTAGCTAAGGA TTGTCAATTTTGTTTTTTGGAAGACCAACGCTTAGCTTTACTGATCTCTTGTATT GTTTTTCTAATTTCTATTTCATTGATTTTTTGCTCTGAAATGTTTCCTTTCTTCCACTAAC TTTAGGCTTAGATTGTTCTTTTTACTAATTCATTGAGGAGTAACATTAAGTTGTTTAT TTAAGATCTCTCTCTCTCTCTCTCTCTCTTTTTGATGTAGGCATTTAGTGTTACAAA CTTTCCTCTTAGAACTGCTTTTGCTGAATCCTGTAAGTTTTAATATGTTGTTTCCATTTT CATTTTTCTCTAAATATTTTTAAAATTAATTTTTTGAATTTCCTCTTTGACTCAATAGTTT TTCAGGAGCATGTTGTTTAATTTGCATATACTTGTTAATTTTTCTTGGTTTCTCCTGTTA $\tt TTGATCTATAGCTTTATATCATTGTGATTGAGAAAGATACTTGATATAATGTTGATCTTC$ TGACACTTGTTAAGATGTTTTGTGGTCTATCAATTGATTTATCCTAGTGAATGTTACATG TATACTTGAGAAAAATGTATATTTTGTTGCTGTTGGATGAAATGTTCTGTATAGGTCTAT TAACTCCATTGGTATACGTATAGTTCAAGTCATATTTTGTTATTAAAAATTTTTTTGTCTA GATAATAGTTCTGTTGTTGGAAGTGGGATATTAAAATTATTTACTATTATTGTGCTGCAT TTATGTCTCTTTTCAGAACTCTTAATCTTTGATTTATATATTTTAGGTGCTTCAGTGTTGG GTGCATATATTTACAATTGTTATATTATCTTGATGCACTGATCTTTTTATTATAATAT ACTGACCTTCTTTATCTCTTTTTACAGTTTTTTTTAACCTAAAGTTTATTTGGTGTGAAA TAAGTATAGCCACCCTGCTCTGTTTTATTTGCCTGGAATATCATTTTCCATCACTTCAT TTTCAACCTGTAAGTTTCCTTTAAGGTAAGGTGAGTCTTCTGTAGGCCCATATAGTTGGA TCTTGTTTGGTATGTATCATGGTACTGTATGCCTTTTGACTACAGAATCTAATCCATTAA ACTTTAAAGTAATTATTGATAGATGAGAGGTTGCTACTTCCATTTTATTGTTTTCAAGTT CTTTTTGCAGGGATATATTTTGAATTTTTTAAAATATTTTTGTGTATCTATTATAGGCTCA TGCTTTGTGGTTACATAAATCATCTTATACCTATAACAAGCTATGCCAAGTTGATAACAA CTTAAGTTTGATCACTTACACAAAGGCTACACTTTTACTCTCCTCCTTCTAAATTTTATG TTTTTGATGTCATTCTTTACATCTTTTTATAATATGCATACTTAACAAACTACTGTAGCT GTAGTTGCTTTTAAGAATTTTGCCTTTTAACCCTTATACTAGAGAAATCCTTGATTTGTT CACCATCATTACAATATTAGAATGTTTTGGAATTGAAAAATGCCATTAATTTTACCAGTG CGTTTTATACTTTCATATGTTTTCATGTTTTCTATTTTGAATCCTTTTCCTTCAGCTTGAA GAACTCCCTTTAGCATTTCTTATAACGCAGGTCTAATGGTGAGAAACTCAGCCTTTGTTA CTCTGAGAAAGTCTTTAACATCCCTCATTATTTAAAGACAGGTTTGCTAGGTATACTATT CTTGATTGGCAGGTTTTTTTTTTTTTAGAATTTTTGAATATTATCCCACTCCCTTGAGCT TTCAAGGTTAATGCTGAGAAATTTGCTGATAGTTTTATCAGGGTTCTCTTATATGTGACA ATTCAATTCTCCCTTGCTGCTTTCCATACTCTAAGTTTTGACAGTTTTGTTATGATGTGC CTTGGTGTGAGTTTCTTTTCCTTTTTTAAATTTTAGATTCAGAGGGTACATGTGCAGATT TGCTGCAAGGACATATTGTGTGGGCGTTGGGCTTCTGTTGATCCCACCACTCAAGTGGTGA CTTTTTCCCTTTTTGGAAGATGCAGTGTCAATTGTTTCTATATTTATGTCTGTGTGTACC ${ t CAATATTTAGTTCCTACTTATGTGAAAGAACATGCAATATTTGGTTTTCTGTTTCCGTGT}$ TAATTTGCATAGGATAATATTTTCCAGTAGTCTGTCCATGTTGCTGAAAAAGACATGAGT TTGTTCTTTTTTATGGCTTCACAGTATTTCATGATGTATATGTACTTGGTGTGGATTTAT CCGGATTCATTTTATTTGGTATTCTTTGGGATTCCTGTATCTGGCTTTCTATTTTCTTCC CCAGTACTGGGAAATTTTCTGCCATTATTTTTTGAATATGTTCTGTGCTTGTCTCTCT CCTCCTTCTGAACACCTATAATGTATATTTGCTCTGATTGAGGGTGTCAGTATGTCTCT TAAGATGTGTTCATTCTTTTTCCTTTTTTCCTTTTTTGCTGCTTAGATTGGATGATTTC CAGTGACTTGTCTTTGAGTTCATTGATATTTTCTTCTGCTTAATCTCATTTGTGGGTGAA CTTTCATATACTTTCTCTTTGTTAAAGTTCTCTGTTTTTGCATTTCTCTCTGGACCTTAG TGACAGTCTTTATAATCATTATTTTAAATTCTCTATTGGGTAAATTACATCTCTTCTATT TCTTTAGTTTCCTTGACTCTGTGTTGTTTACTGCACATTAGATAAGACAGCTGCCTTTCC CAGTCTTATCAAACAGGACCTGTGTAGAAGAAAAATATCACTAGTCCATTTGACAAAAAA $\tt TTTTAATGTGCCTCTCAAAGCTTTGTTTGTCCAGGCCACTGTTTCTGTTATTGGTGGCTC$ CCAGGAGATTGGGATATGCCATGTCCTATCAATACTCTGTGAACTATAAGATAGAGGCCA

FIG. 1AX

51/51

GACTTTCAAAATGTAGCCAGAAAAATGTCAAGTATTAGATGTGTGGTCCAGTTCCTTCTA AGAGGTACTATGGAAACTGCCTGTATTTGTGTTCAGGCCACACTTTTTGATTCTGGGAAG ATAGCTTTGGGAGTGGGGCCACTGTTTGTCTACATCTTTGTTATCTGTGATCTAGAGTAA GTTAGGAATGCAAAGCTCCACCACTCCCAAGCTTAGGCTGTTAAGAATTCAGTCCTTTGG GTGGGAGCTGTAGAAGTTGTGACACTTAATTGTGAACAAACTCTTTTCAAGAAGAATAGG TAGGCTATAAAATAATAGAAGAAATGAATAGAGCTATAGAAGTTGTGACACTTGGTATGT GAACAACTCCTTTTAGGAAAAATAGGCTGGGGACAAGCCAAGTTCTGCTTAGTCTACCT GAGAGCTACTATTAGTCTGTCTTGTTAGCTCCCTGATGCAAGCTGGAGGTTAAGCTATGT ATTCTAGCCCCTGTTCTCCACTGCTCCCAAGAGATATAGTTCCTGGAAGAGTTTGCATGC CTGTTTAAAACCACCTCTTTGTTCTGTGATCTAGGGAGACTTGTATATGCCTAGTCTCTT CTGCTCTTAGAGCCAGGAGTTTTGGGATATAGTATTTCTGGTAAATGCTGTAAAAGGGCA TTTTGTGGGTGAACACACTCCTTCCAGGGAGAATTGGGAGAGCTGGGATTATTGCTGAGT TGAGCTGGAGGAAGTCTCAGGAAGTGTTAAGCTGCTGCTCAGGCTGTTAGAGAGCTACTT TTTGCTTGCCCCTTTAACTCTCAGATGCGTTAGTTAGAAACCAGACTGTCAAGTAGCCGC TAGGGGAGTATGCTGTAAACCTCTTCCAGGGAGAACCAGGTAGTGGTATTTTTGAGTCCT GTCTCTGTACTAATTCTACTAATTCACAGTGTTAAAGCACCTGAAAAAGTGCTTGCACAC TCTAACTCCCAGAGTTGGTGAATTAAGAGCCAAACTGTTGGGCATCTTATAATTGGGGTG CCATATGTAAGGTCCCAATCCTCTCCACAGGGAGAATCTGAGTGTTAGTGATTCCAGTTA TATGGTGAAGTACCTGGAAGGGGTCCATGCTCAAGTATGCCTCAGATTTGTCTACCCATT GAGACAGAGTCTCATTCTGTTGTAAAGGCTAGAGTGCAGTGGCACAATCTTGGCTCACTG CAGCCTCTGCCTCCCTGGTTCAAGTGATTCTCCTGCCTCAGCCTCCCGAGTAGCTGTGAC TACAGATGCGTACCACCATTCCCAGCTAATTTTTTGTATTTTTTGGTAGAGACAGGGTTTCA TCATGTTATCCAGGCTGGTCTCAAACTCCTGGACTCAAATAATCCACCAGCCTTGGCCTC GATGTTCATTCTGTGCATTTGTGAGTATTGGGAGTGCCAGGAGCTTCCTATTCTGCCATG TTGCTGACATCAGTCTAAGGAAAACAGTTTAAAGGAAAGTTCATCAAAAAGTAACAGTAGA CTTTCTTTCTTTCCTTCTTTTCTTCCTTTCC

FIG. 1AY